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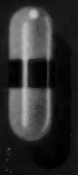

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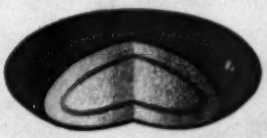

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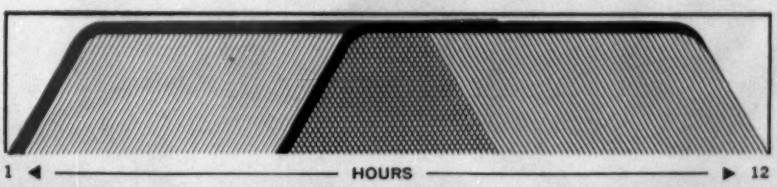

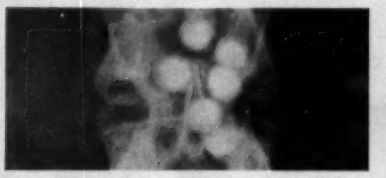

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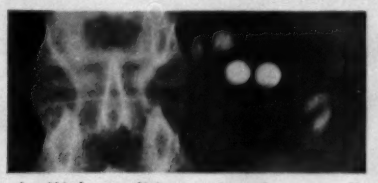

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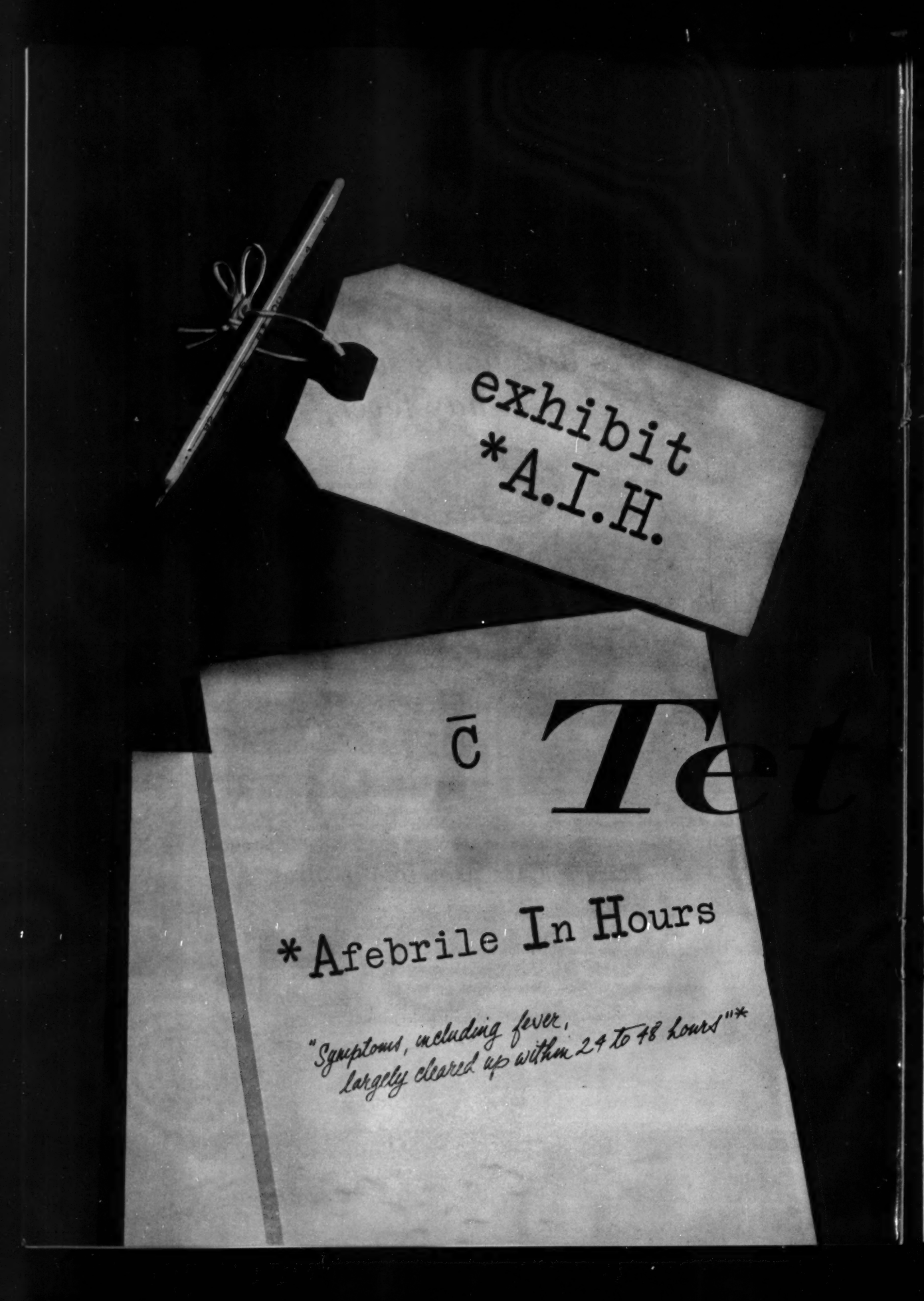
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**English, A. R., et al.: Antibiotics Annual (1953-1954), New York, Medical Encyclopedia, Inc., 1953, p. 70.*

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Meats-in-a-Can

and Kitchen-Cooked Meats... Comparative Nutritive Values

From a practical dietary standpoint, meats-in-a-can—preserved by commercial canning—are nutritionally interchangeable with meats of like variety prepared in the home.[1] For taste appeal, for economy and "keeping" quality, and for household convenience, meats-in-a-can are advantageous in many respects.

As the comparative data here shown indicate, kitchen-prepared meats and similar meats-in-a-can are closely alike in the amounts of various nutrients they provide.

COMPARATIVE COMPOSITION OF KITCHEN-COOKED AND COMMERCIAL-CANNED MEATS
(Nutrient Amounts per 100 Grams)

	*Kitchen-Cooked Ham[2]	**Canned Ham[3] (Chopped, Cured)	Kitchen-Cooked Beef Round[2]	Canned Roast Beef[2]
Water	50%	50%	59%	60%
Protein	21 Gm.	20 Gm.	27 Gm.	25 Gm.
Fat (ether extract)	28 Gm.	20 Gm.	13 Gm.	13 Gm.
Niacin	4.0 mg.	4.3 mg.	5.5 mg.	4.2 mg.
Riboflavin	0.21 mg.	0.19 mg.	0.22 mg.	0.23 mg.
Thiamine	0.46 mg.	0.40 mg.	0.08 mg.	0.02 mg.

*Values after conversion from 42% to 50% water basis.
**Values after conversion from 58.69% to 50% water basis.

Experimental studies have shown that the processing which meats-in-a-can undergo leads to little if any greater vitamin losses than does home-cooking of similar cuts of meat. In general, meats-in-a-can retain of their original vitamin content approximately:

60 to 80 per cent of thiamine
90 to 100 per cent of riboflavin
90 to 100 per cent of niacin
80 per cent of biotin
70 to 80 per cent of pantothenic acid.[4,5]

During storage for customary periods, at usual warehouse temperatures, meats-in-a-can show little, if any, further vitamin loss except in thiamine. Even thiamine, a highly thermolabile vitamin, was 52 per cent retained in pork-in-a-can after ten months' storage at 80° F. Retention of the vitamin was notably greater when the canned pork was stored at 38° F.

Since meats-in-a-can are thoroughly cooked in processing, they may be consumed as purchased, merely warmed or mildly cooked. When the meat is moderately cooked in preparation for consumption, little or no further loss in vitamins need to occur.

Recent studies show that meats-in-a-can are excellent sources of needed amino acids.[6] The 18 amino acids determined in these studies appeared in similar ratio and amounts in canned beef, pork, and lamb as in the respective fresh or home-cooked meats.

1. Howe, P. E.: Foods of Animal Origin, Handbook of Nutrition, American Medical Association, ed. 2, Philadelphia, The Blakiston Company, 1951, p. 637.
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4 Hypotensive action is independent of alterations in heart rate.

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8 Cardiac work is not increased, tachycardia is not engendered.

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13 Because of its rapidly induced, prolonged action (6 to 8 hours), tablets Veriloid provide around the clock hypotensive effect from 4 doses daily, make today's dosage effective today, and usually prevent hypertensive "spiking" during the night.

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1. Kauntze, R., and Trounce, J.: Treatment of Arterial Hypertension with Veriloid (Veratrum Viride), Lancet 2:1002 (Dec. 1) 1951.
2. Wilkins, R. W.: Combination of Drugs in the Treatment of Essential Hypertension, Mississippi Doctor *30*:359 (Apr.) 1953.
3. Stearns, N. S. and Ellis, L. B.: Acute Effects of Intravenous Administration of a Preparation of Veratrum Viride in Patients with Severe Forms of Hypertensive Disease, New England J. Med. *246*:397 (Mar. 13) 1952.
4. Moyer, J. H., and Johnson, I.: Intramuscular Veriloid (Aqueous Solution) As a Hypotensive Agent, Am. J. M. Sc. *226*:477 (Nov.) 1953.

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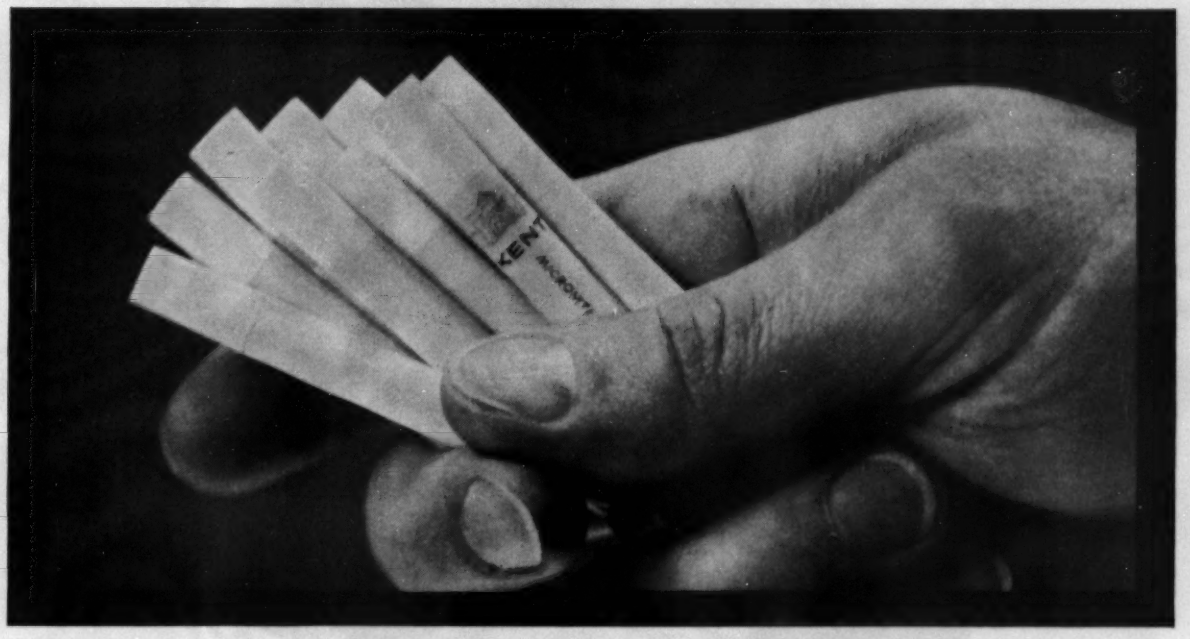

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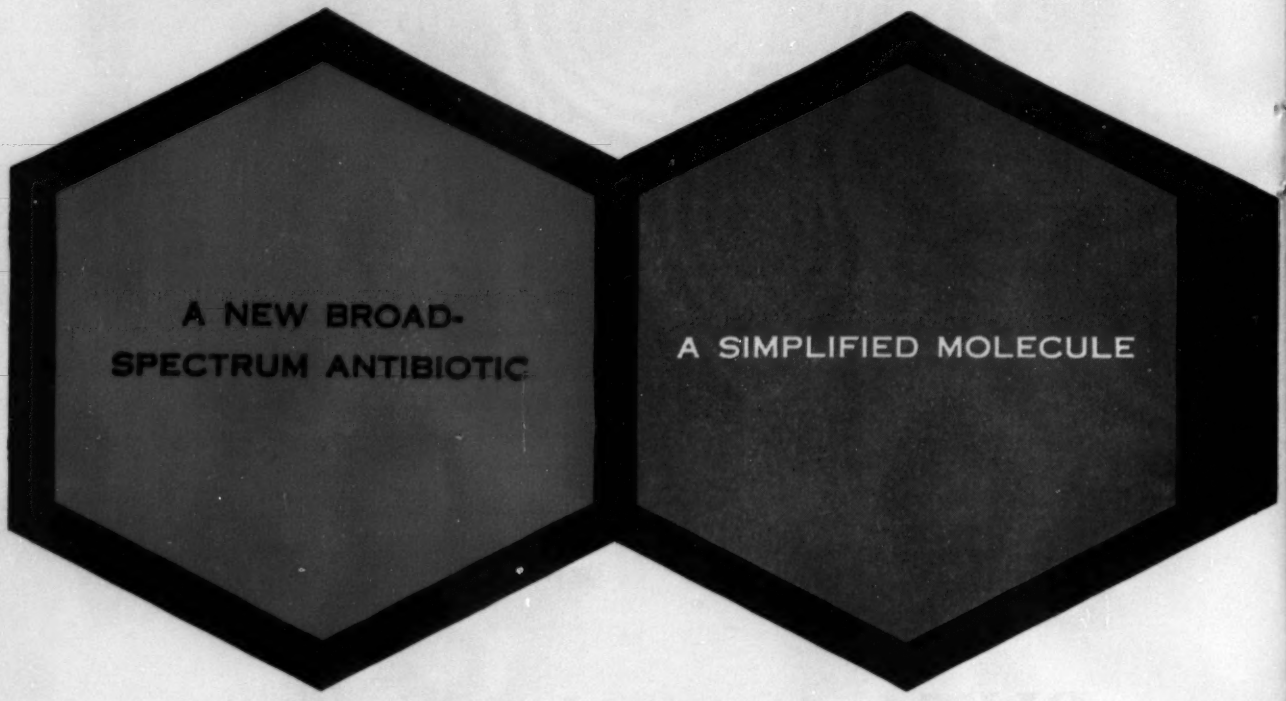

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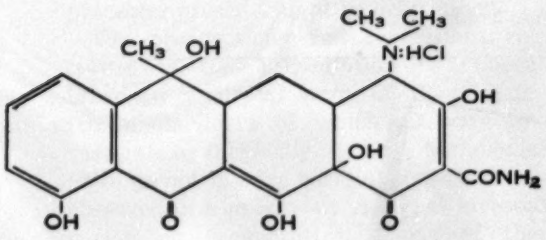

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FROZEN SHOULDER*

ANTHONY F. DE PALMA, M. D.,**
Philadelphia, Pa.

The enigma of the "frozen shoulder" has been a challenge to our profession for many decades. Many and varied premises have been advanced relative to the etiologic factors and the pathogenesis of this disorder. A critical survey of the literature leaves the reader confused and bewildered because it fails to provide convincing evidence concerning the causative factors and the pathologic processes involved. It was interesting to note that most observers focus their attention on one particular area of the scapulohumeral joint believing it to be the responsible agent for the malady. Duplay believed that inflammation of the subacromial bursa was the causative agent, others centered their attention on the capsule of the joint, particularly the inferior redundant portion and still others tried to incriminate the coracohumeral ligament and the biceps tendon. It becomes apparent that the lack of information and the erroneous premises recorded stem from the failure of surgeons to explore surgically a large series of shoulders affected by the malady in order that the true nature of the pathologic processes present might be determined.

The observations and conclusions recorded in this presentation have been based on a clinical study of 72 cases of frozen shoulders of which 42 were investigated surgically. The pathologic findings noted were correlated with those observed in a previously reported investigation on degenerative lesions of the shoulder joint in various decades. This correlation permitted one to reach the following conclusions: (1) the pathologic process present is a diffuse inflammatory process of varying severity implicating all the soft tissue components of the scapulohumeral joint and it is not restricted to a specific region of the joint; (2) the biceps tendon and its sheath are implicated in all instances, the involvement may be primary or secondary in origin; (3) pain associated with a frozen shoulder is primarily the result of a tenosynovitis of the biceps tendon and the pain factor is more distressing than the stiffness; (4) if pain is eliminated restoration of function can begin which in turn will cause a reversal of the pathologic process permitting the tissues to return to normalcy; and (5) manipulative procedures, as a form of treatment, are futile and even harmful.

In this series only one case was under the age of 40 years. In the light of this information it becomes apparent that some factor must be present in the older age group before the syndrome can develop. The responsible factor comprises the degenerative changes present in all the elements of the shoulder joint after middle life. In a previously recorded study it was definitely shown that degenerative alterations were first manifested in the second decenium and that they increased in gradient with each successive decade. The changes implicated all the components of the musculotendinous cuff, the synovialis, the articular cartilage of both the glenoid cavity and the head of the humerus and the biceps tendon; they were demonstrable both macroscopically and microscopically. In the first four decades they were minimal in intensity; after the fourth decade they increase markedly in severity.

ONSET OF SYNDROME

In 47 cases the onset was insidious in nature with no history of injury to the

*Read before the Medical Society of Delaware, Wilmington, October 13, 1953.

**Professor of Orthopedic Surgery, Jefferson Medical College.

affected extremity; in 11 the syndrome followed direct trauma to the shoulder and in 14 it was a sequal to injuries at a distance from the shoulder as the wrist, elbow or forearm. Regardless of the cause, all cases exhibited a common denominator; namely, muscular inactivity in varying degrees. It soon became apparent that in the presence of degenerative abnormalities, muscular inactivity was necessary for the evolution of the pathologic processes which culminate in a frozen shoulder.

PAIN

The pain factor is the outstanding symptom in all cases of frozen shoulders. It is accentuated by specific movements of the scapulohumeral joint particularly abduction and external rotation and backward flexion. As in bicipital tenosynovitis the pain may be projected to the belly of the biceps muscle, the anterolateral aspect of the shoulder region, the flexor surface of the forearm and the inferior angle of the scapula. Pain, particularly in advanced cases, is often most severe at night interfering with the patient's sleep. Objectively, in all the cases in this series, tenderness was elicited when pressure was made over the intertubercular sulcus and when the biceps tendon was rolled under the examiner's thumb. This observation is clinical presumptive evidence that the biceps tendon is implicated in the pathologic process present and further suggests that involvement of the tendon and its sheath is the chief agent responsible for the pain. This premise is supported by the observation that those movements of the scapulohumeral joint which permit greater excursions of the humeral head on the tendon are accompanied by accentuation of the pain.

It was interesting to note that with increase in the intensity of the pain the arcs of motion at the scapulohumeral joint become progressively smaller until little or no motion was demonstrable, in most instances a few degrees of motion are discernible in the anteroposterior plane.

COURSE OF THE DISEASE

The clinical course pursued by this disorder is unpredictable but it is guided by some obvious factors. In some patients the syndrome terminates spontaneously; this may occur early or late in the disease; and in a small group the malady exists indefinitely; three patients in this study exhibited an active syndrome three, six and eight years respectively with no evidence of improvement. It was interesting to observe that in the patients in which recovery occurred in the early stages, the pain factor was never so severe as to cause severe impairment of scapulohumeral motion; in these, muscular inactivity was maintained at a minimal level. The individuals in this group, as a rule, disclosed good muscular development and were in relatively good general health. On the other hand, in the group in which recovery was achieved late in the disease, the general health was poorer than in the first group. This was determined by the patient's muscular development, nutrition and the presence of debilitating factors as cardiac or pulmonary diseases. Muscular inactivity and atrophy were outstanding features in this second group. These observations lead one to conclude that muscular activity which is responsible for and maintains normal tissues metabolism is a necessary function to abort or reverse the pathologic processes responsible for frozen shoulder; however, the extent of normal muscle action is governed by the intensity of the pain; the greater the intensity of the pain the less the patient employs the arm; restoration of normal motion is only possible when pain is reduced in intensity or is eliminated. It is erroneous to believe that complete recovery will be achieved in all cases of frozen shoulder with or without treatment in six to 36 months. This series reveals that in many of the patients residual objective findings are discernible; these comprise some loss of motion in abduction and external rotation and varying degrees of weakness in the extremities. Also, it was previously noted that three patients in this series exhibited a painful frozen shoulder, the duration of which was three, six and eight years respectively.

PATHOLOGY

The gross and microscopic findings observed in 42 cases of frozen shoulders which were explored revealed that all the tissues were implicated in a low grade inflammatory process. This included the capsule, synovialis, facial coverings, musculotendinous cuff, biceps tendon and sheath and the subacromial bursa. The severity of this process was in a measure governed by the age and general physical status of the patient and the duration of the disease. In general, the process comprised marked edema of the tissues, degeneration of the collagenous fibers, pronounced round-cell infiltration, increased vascularity, thickening of the synovial membrane and increased fibrosis. All the involved tissues lose their elasticity and become shortened, contracted and fibrotic, thereby fixing firmly the humeral head in the glenoid cavity. In severe cases the tissues are extremely friable and tear readily if the humerus is abducted or rotated externally; this is particularly true of tissue on the anterior aspect of the joint. The coracohumeral ligament is converted into a stout, thickened contracted cord. The shortened subscapularis tendon together with the coracohumeral ligament constitute powerful checkreins to external rotation of the head of the humerus. Normally the capsule and synovial membrane along the inferior and anterior aspect of the head of the humerus fall into nictating folds, these become adherent firmly to the bone by numerous adhesions of varying consistency and strength.

The most significant finding was the implication of the tendon-tendon sheath gliding mechanism of the biceps tendon in all the cases explored. The intensity of the inflammatory process varied considerably. In some the tendon lay in a mesh of adhesions while in others it was firmly anchored to the bicipital groove and to the undersurface of the capsule, particularly in the region of the intertubercular sulcus; in seven cases the tendon was so firmly adherent to the floor of the groove that it could be released only by sharp dissection and in two cases the tendon had attained a bony anchorage. It became apparent that nature was trying to obliterate the gliding mechanism of the tendon by attaching the tendon to the shaft of the humerus. When these observations were correlated with the objective clinical features it becomes obvious that involvement of the biceps tendon is the agent responsible in a large measure for the pain in these cases, particularly when the arm is put through arcs of motion which require a wide excursion of the humeral head on the tendon. This concept is further substantiated by the observation that when the gliding mechanism was obliterated by surgical intervention dramatic and instantaneous relief of pain ensued.

That obliteration of the tendon-tendon sheath gliding mechanism is one of nature's methods of alleviating pain and permitting restoration of function is illustrated by the following case. A male, J. F., age 73, was examined three months prior to death. No clinical dysfunction of either shoulder was demonstrable and the patient was unaware of any disability in either extremity. From his history it was learned that 15 to 17 years prior to this examination he suffered severe pain and limitation of motion, first in the right and then in the left shoulder joint. After an indefinite period of time (two to three years) the pain subsided gradually and restoration of function was restored in both shoulders. From the history and restriction of motion associated with pain, it is reasonable to assume that a frozen shoulder had existed in either extremity. After death both scapulohumeral joints with the musculotendinous cuffs intact were removed and studied. The intracapsular portions of both biceps tendons were absent while the extracapsular portions had attained a bony insertion below the lesser tuberosities. Hence, nature had achieved a cure by deleting the gliding mechanism of the biceps tendon.

PATHOGENESIS

It becomes apparent that muscular inactivity, regardless of the cause, in the presence of degenerative alterations found in patients past middle life may initiate

the syndrome; the most common cause producing muscular inactivity is bicipital tenosynovitis; in this series it was estimated to be the causative factor in 65 per cent of the cases.

In the wake of muscular inactivity regardless of the cause varying degrees of muscle atrophy ensues. This in turn, is followed by a disturbance of the metabolic processes of all the soft tissues about the shoulder joint which induces slowing of the circulation and venous and lymphatic stasis. The musculotendinous cuff and all the adjacent tissues become saturated with serofibrinous exudates which provide fibrin producing capsular, synovial, fascial intermuscular and intramuscular adhesions. All tissues are involved simultaneously as is revealed by study of microscopic sections made from the aforementioned tissues at different phases of the disease.

At this point an explanation of the different courses that the diseases may pursue is in order. It is general knowledge that in many cases, after varying periods of pain and dysfunction, pain disappears or subsides and restoration of joint function follows. In these instances it is reasonable to assume that the inflammatory process subsides and resolution of the adhesions, particularly those involving the biceps tendon, occurs. With the diminution of pain, muscular activity is restored, which in turn, allows normal circulation to the affected tissues. In other instances the course is a protracted one and may remain static for many months. In this group the chronic inflammatory process persists, and the biceps tendon remains imbedded in adhesions and is the source of continued pain and dysfunction. Finally, there is a group of patients in which after a long disabling siege, pain disappears eventually and function returns slowly. In this last category the patients are relieved of pain because nature succeeds in providing the biceps tendon with a new bony attachment to the shaft of the humerus, thereby obliterating the tendon gliding mechanism.

TREATMENT

In the light of the aforementioned observations, the aims of the treatment of frozen shoulders are (1) relief of pain and (2) restoration of normal muscular function. Conservative measures will affect a cure in a large number of cases both in the early and late stages of the disease, particularly in the former. In this series 17 of 28 cases in the early stages and 11 of 44 cases in the late stages responded to conservative management. This comprises measures to improve the general health, hot fomentation of the shoulder region, a regulated program of gravity free exercises within the painless arcs of motion and sedation. Blocking of the sympathetic ganglia also is a valuable adjunct in relieving pain and muscle spasm. Later antigravity exercises such as crawling up the wall, using the pulley and the wheel are added. If after a fair trial with conservative measures, the patient fails to respond, then surgical intervention is justifiable. This consists in obliteration of the biceps tendon gliding mechanism by anchoring the tendon either to the coracoid process or the shaft of the humerus. I prefer the former; the intracapsular portion of the tendon is also removed. Transplantation of the biceps tendon does not increase immediately the range of motion in the scapulohumeral joint. However, this procedure eliminates the pain factor and now muscular activity can be initiated. Optimum function is attained in two to four months.

MANIPULATION OF FROZEN SHOULDER

Manipulation of frozen shoulders is a dangerous and futile procedure. That this is true was confirmed by the observations noted in 11 cases which were manipulated under direct vision. The affected shoulders of these 11 cases were exposed through an anterior deltoid splitting incision. In all instances when the arm was externally rotated, regardless of how gently the maneuver was performed, tears of varying degrees were noted in the subscapularis tendon and in its lower muscle fibers inserting into the shaft of the humerus. In two individuals the tendinous insertion

of the subscapularis muscle was completely avulsed from the lesser tuberosity, and the tear extended proximally into the musculotendinous cuff 1 and 1½ inches respectively. Abduction of the arm in all cases produced transverse tears in the fibrous capsule along the inferior aspect of the neck of the humerus. In three instances the articular surface of the head came into view through tears in the capsule. In three instances rupture of the biceps tendon at the level of the intertubercular sulcus was sustained, and in one, fracture of the surgical neck resulted.

Such observations point out the hopelessness of such a procedure. One is forced to conclude that the cases that are benefited by manipulation may be those in which the tendons of the long head of the biceps brachii muscles were ruptured.

By so doing, the tendon-tendon sheath gliding mechanism is obliterated and pain is eliminated. As previously noted, nature often resorts to this method by anchoring the tendon to the shaft of the humerus.

CONCLUSIONS

1. Frozen shoulder is a clinical entity which is produced by muscular inactivity of the shoulder in individuals past 40 years of age.
2. Bicipital tenosynovitis is the most common etiologic factor producing muscular inactivity. (It initiated the syndrome in 65 per cent of the cases in this series.)
3. Pain is the outstanding clinical feature of frozen shoulder; once pain is eliminated, restoration of function can begin.
4. Conservative measures in early cases may abort the syndrome.
5. In late cases transplantation of the tendon of the biceps muscle to the coracoid process will eliminate the pain factor and permit painless motion in the shoulder joint.
6. In this series optimum restoration of function was obtained in from eight to 22 weeks.
7. Manipulation of the frozen shoulder is a futile procedure; the only cases that benefit from this method of treatment are those in which the biceps tendon is ruptured at the time of manipulation.

7037 Greenhill Road

DISCUSSION

DR. A. R. SHANDS (Wilmington): Dr. DePalma is an authority on what he has told us. Those of you who know him in Philadelphia and are familiar with his work will, I am sure, concur in this statement. The perfectly beautiful specimens of which he showed us slides are ones taken from his collection from the Department of Anatomy of the Jefferson Medical College, and are certainly the very best that I have ever seen.

I am delighted that he has emphasized particularly this point about the futility of manipulation. Going back about thirty years, when I got into orthopedics, we were taught to manipulate these frozen shoulders, and we certainly were not cautioned to manipulate them with care. We younger ones were always impressed with the extreme pain the patient suffered following manipulation, and in following through with many of these patients, certainly the results were much worse than they were when they started.

I think what De DePalma has told us about the 65 per cent of these cases having an involvement of the tendon sheath of the biceps is very significant. I did not realize that it was as high a percentage as this and that this is perhaps the key to the pathology in most of these shoulders.

There is no doubt that pain is the most salient point and that once pain is relieved by injection, or heat, massage, or sedation, as he has told us, you can do a great deal in loosening up these shoulders with gentle exercise and with gentle measures.

DR. D. J. KING (Wilmington): I have always found it a pleasure and extremely informative to hear Dr. DePalma speak on the shoulder. I had one interesting experience some time ago when I saw six frozen shoulders. It seems that in the past the patients had been advised that rest was cardinal for their recovery. This apparently included shoulder inactivity,

and they developed frozen shoulders and then pain. They all had the typical picture of atrophy.

We suggested activity, that the patients wash their own hair, do their own shampooing, and it was agreed that such rigid rest wasn't necessary.

I would like to ask if compound F has a place in the conservative treatment of the frozen shoulder. I, too, was brought up in the school that taught manipulation of the knees and hips as well; however, we were warned — and my time does not go back as far as Dr. Shands' does — to be extremely careful and to manipulate only a few degrees at a time, and do repeated manipulation, and if a very gentle manipulation ended up with a severe pain and added disability, to stop.

I wonder if in manipulations of the knee and hip we sometimes don't lose something?

DR. W. L. BAILEY (Wilmington): I want to bring this up. There are various departments of roentgenology around Wilmington that have patients for roentgen therapy of so-called subacromial bursitis, where the patients are given roentgen therapy for the subacromial bursitis without any attempt to make a diagnosis, namely, without taking pictures of the shoulder.

I believe that shoulders which are symptomatic and which do not have calcium appearing in their x-rays are probably not cases of subacromial bursitis. In people, particularly in the older age group, in whom shoulders are symptomatic, it is probable that they are suffering from what we have seen here, and I do not believe that x-ray is effective, and I believe that we are actually losing valuable time in the treatment of the shoulder. I wonder if Dr. DePalma would comment on this?

ACTING CHAIRMAN DOBSON: Dr. Bailey's question is very interesting to me, too. We freqeuntly refer these patients, and I never know for sure whether I am giving psychotherapy or whether we are doing any good. I would like to hear Dr. DePalma's comment on that.

Doctor, would you close the discussion?

DR. DEPALMA: I purposely failed to mention compound F in the treatment of frozen shoulder because I knew someone would ask about it.

If you recall, several years back there was a presentation at the Academy in which there was much to do about the treatment of frozen shoulders with compound F, or rather, with cortisone. I returned immediately to Philadelphia and put a whole series of patients on cortisone. Our conclusion was that these patients, all of them, benefited generally — their general health improved and they felt better — but in no instance did we think that the patients had made the recovery they had exhibited, that they would not have made had they just been given simple sedation and simple therapy.

We went to the next step, and that was the local injection of compound F. I have not been convinced in my own mind that I have helped patients sufficiently to recommend it as a routine procedure. There is no doubt that in some instances when it is injected locally these patients state that they feel better, but as you know, you all can inject simple saline in some of these patients and they will feel better.

So I do not think that the local injection of hypercortone, or giving the cortisone by mouth, in my series of cases has been of such a value as to put these patients routinely on this type of therapy. In fact, I don't use it at all.

Now I come to the problem of bursitis and calcareous tendinitis. I always try to eliminate discusssion on bursitis and calcareous tendinitis because I invariably make a statement which rubs the roentgenologist the wrong way and I stick my neck in a noose.

In the first place, I do not believe that there is such an entity as a primary bursitis. The only time that an individual obtains a lesion of the bursal sac it is secondary to something else in the shoulder. When a patient does have a calcareous deposit in the rotator cuff, the only time that the subacromial bursa is implicated

is when the deposit ruptures and it goes into the adjacent subacromial bursa.

Now, when that happens, the patient's pain is gone, gentlemen. Anything that will rupture that calcareous deposit and acute calcareous tendinitis will give the patient relief from pain. Whether it is exercise, whether it is needling, whether it is x-ray therapy, or what not, once the deposit is ruptured the patient is relieved of his pain. How often have you had patients on whom you were going to operate — it has certainly happened to me — who had excruciating pain the night before, and the next morning the patient says in the hallway, "Doctor, are you going to operate on me? The pain is gone." And when you do operate on the patient you will find that the deposit has ruptured and the calcareous deposit, or part of it, is now free in the subacromial bursa.

I feel that x-ray has no place in the treatment of either bursitis or calcareous tendinitis. I have seen so many cases exposed indiscriminately to x-ray therapy with no justification, because first of all, the diagnosis was never established, and secondly, I know that the only time that the x-ray will help the patient with calcareous tendinitis is when the deposit is about to rupture, and it would be very interesting if you held off the x-ray for a couple of days to see if the patient would have gotten better anyhow.

SIMPLE METHOD FOR CONTROL OF VAGINAL DISCHARGE RELATED TO CARCINOMA OF THE CERVIX

DOMINIC J. PONTARELLI, M. D.,
Philadelphia, Pa.

One of the most common forms of cancer found in the multiparous female is carcinoma of the cervix. The disease occurs in all age groups, most frequently in women 40 to 54 years, and rarely in patients under 20 years of age.

Carcinoma of the cervix is frequently accompanied by a chronic vaginal discharge, which is foul smelling and is irritating to the vaginal mucous membrane. The odor ascribed to the discharge probably results from small fragments of necrotic tissue and from a very high bacterial count.

Laceration of the cervix with subsequent bacterial infection is probably the most common cause of vaginal discharge. It is due to neglect and improper treatment that this condition often precedes a carcinomatous lesion. Obstetrical trauma and negligence in the treatment of tears have been considered contributing factors in the establishment of carcinoma of the cervix. It has been estimated that only about 35 to 44 per cent of the patients with carcinoma of the cervix have a five-year survival.

Patients with *active* carcinoma continue their existence uncomfortably; the vaginal discharge persists and the characteristic foul odor prevails to haunt them. Treatment of the disease with radium and x-ray produces radiation changes in the vaginal mucosa which predispose to slough formation, discharge and bacterial invasion.

Assiduous observations and an abundance of rational clinical experience have convinced us that after radiation it is our duty to the patient to make her comfortable and to blunt the intensity of the pathologic process to the best of our ability. There is no denying that it is impossible to control the process, let alone "cure it" in all of the patients.

Since our purpose must be the establishment of a regimen which is therapeutically valid, we made a search for a therapeutic procedure which would accomplish at least three things: (1) control the bacterial infection and eliminate the discharge; (2) eliminate the foul odor, and (3) give the patient a high degree of comfort. We postulated that if these criteria could be realized, the patient's existence would at least be tolerable and our duty substantially fulfilled.

A vaginal cream containing allantoin, 2%; sulfanilamide, 15%; and 9-aminoacridine, 0.2% in a water-miscible base with an acid pH*, was selected for our

*Allantomide Vaginal Cream Improved, supplied by the National Drug Company, Philadelphia.

study since it seemed to have the capacity to realize the objective we established.

Allantoin, according to Tremble,[1] appears to act in three ways: (1) it has a digestive-like action on pus or necrotic tissue; (2) where healing is slow, it stimulates proliferation and tends to produce healthy pink granulating tissue; and (3) it has a synergistic action with sulfa drugs. In its presence bacteria which have become sulfa-fast are resensitized to the action of sulfonamides.

Saralegni and Villaneuva[2] concluded that "Allantoin and Sulfonamide mixtures stimulate phagocytosis, accelerate the elimination of substances which inhibit healing, prevent the harmful effects of sulfanilamide and stimulate cell proliferation and formation of new tissues."

There is a voluminous literature on the bacteriostatic activity of sulfanilamide in contaminated and infected wounds; however, we do not deem it essential to this report to offer a review of this literature.

A combination of allantoin, 2%; sulfanilamide, 15%; and lactose in a water-miscible cream base adjusted to an acid pH, was introduced by Park[3] for the treatment of infections of the cervix, vagina, and vulva. The therapeutic effectiveness of this combination in the treatment of leukorrheas of various etiologies has been attested to by a number of clinical reports.[4, 5, 6, 7]

In order to increase the effectiveness of the Park formula against a broader bacterial spectrum, a colorless flavine, 9-aminoacridine, 0.2%, was incorporated. Unger and Robinson[8] found this compound to be active against not only gram-positive cocci, but also spore-bearing anaerobes and gram-positive and gram-negative bacilli.

The increased effectiveness of the formula containing 9-aminoacridine was clinically demonstrated by Cacciarelli[9] and Cortese and Padovano[10] in the treatment of trichomoniasis. Dill and Martin[11] found the preparation effective in cases of mycotic vaginitis.

Hensel[12] used the new formula with gratifying results in vaginal hysterectomies and in anterior and posterior repairs to reduce post-operative morbidity, to hasten healing, and to decrease the amount and odor of the vaginal discharge post-operatively.

MATERIALS AND PROCEDURE

Clinical diagnosis and laboratory evidence definitely established the existence of carcinoma of the cervix in each of the nineteen patients, ranging in ages from 47 to 71 years, included in this study.

A complete history survey was obtained from each patient, after which a general physical examination was made, with careful attention being paid to the breasts and the abdomen.

After the patient had emptied her bladder she was prepared for a vaginal examination. The characteristics of the vaginal discharge were noted (there was no necessity to determine the odor). The vagina and cervix were exposed, thoroughly but gently cleansed, and then carefully inspected with use of a speculum. Following the examination of the vagina and cervix, the rectum, sigmoid, and bladder were explored using proper diagnostic instruments, to determine whether or not there was any invasion of these areas. Biopsy specimens were obtained from the lesions for diagnostic confirmation during a dilatation and curretage done in the operating room. We want to stress that every effort was made to cause as little discomfort as possible during these examinations.

The patients were classified according to the standards established by the International Classification (1950):

Stage I—The carcinoma is confined entirely to the cervix.

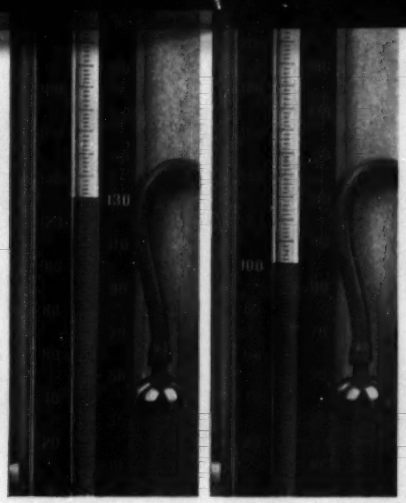
One patient was placed in this category. She developed marked radiation reaction to lateral fornices, extending to upper one-half of the vagina. The vaginal cream was applied twice daily for one week, then once daily for two weeks. The discharge practically disappeared, the odor was controlled and the patient was comfortable.

REPORT ON Apresoline

FROM A STUDY OF 97 HYPERTENSIVE PATIENTS[1]

EFFECTIVE ANTIHYPERTENSIVE

PRODUCT OF CIBA RESEARCH

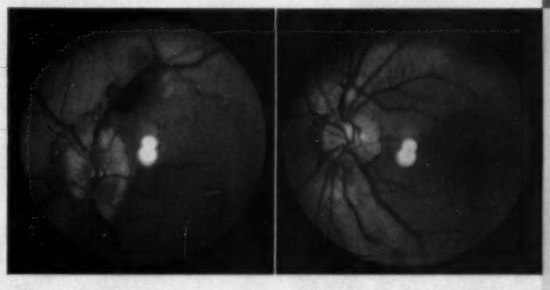


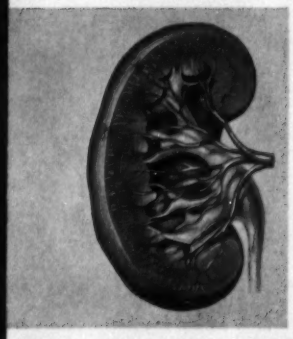
APRESOLINE REDUCES DIASTOLIC PRESSURE

Diastolic pressure reduced to level considered normal in one-quarter and to 110 mm. Hg or less in one-third of 97 patients receiving oral Apresoline for periods ranging from 3 months to 1 year or longer;[1] hypertension in which neurogenic or psychogenic mechanisms predominated most improved; patients with severe as well as moderate hypertension benefited.

APRESOLINE LESSENS RETINAL ARTERIOLAR CONSTRICTION, RETINAL HEMORRHAGES*

Lessening of retinal arteriolar constriction; disappearance of retinal hemorrhages; remittance of hypertensive headaches, giddiness, paresthesias, transient pareses, and encephalopathies; some evidence of improved mental alacrity.





APRESOLINE INCREASES RENAL BLOOD FLOW

Renal improvement less marked than cerebral improvement, but renal blood flow and filtration rate increased and hematuria and proteinuria remitted in some cases; hypertensive heart disease little improved and, in some cases, worsened.

Side Effects: Side effects "minor, transient, or remediable" in most cases. Headache, gastrointestinal upset, periorbital and ankle edema, and a "grippe-like syndrome"—involving malaise and muscle and joint pain (see note)—observed.

Apresoline®

NOTE: Appearance of arthritis-like symptoms during Apresoline therapy is an indication for cessation of treatment. Experience has shown that the phenomenon remits spontaneously on withdrawal of the drug. These symptoms are not likely to occur in patients who receive a daily dose of 400 mg. or less.

FOR COMPLETE INFORMATION on Apresoline ask your CIBA representative or write Medical Service Division, CIBA Pharmaceutical Products, Inc., Summit, N. J. **SUPPLIED:** Apresoline hydrochloride (hydralazine hydrochloride CIBA) 10-mg. tablets (yellow, double-scored), 25-mg. tablets (blue, coated), and 50-mg. tablets (pink, coated) in bottles of 100, 500, and 1000; 100-mg. tablets (orange, coated) in bottles of 100 and 1000.

1. TAYLOR, R. D., DUSTAN, H. P., CORCORAN, A. C., AND PAGE, I. H.: ARCH. INT. MED. 90:734 (DEC.) 1952.

*THE NORMAL FUNDUS (RIGHT) AS COMPARED WITH THE FUNDUS IN HYPERTENSION SHOWING EDEMA, EXUDATES, AND HEMORRHAGES (LEFT): ILLUSTRATIONS FROM "THE FUNDUS OF THE EYE": BEDELL, A. J.: CIBA CLINICAL SYMPOSIA 4:135 (JULY) 1952. THESE ILLUSTRATIONS ARE FOR DEMONSTRATION PURPOSES ONLY AND DO NOT REPRESENT APRESOLINE-TREATED PATIENTS.

CIBA

ALLEVIATES HAY FEVER, OTHER RESPIRATORY ALLERGIES

The above photos show a case of allergic rhinitis before and after Pyribenzamine therapy. Many such cases have been reported in the literature. A few examples: Loveless and Dworin[1] found Pyribenzamine beneficial in 82% of 107 patients; Feinberg[2] noted relief in 82% of 254 cases; Gay and associates[3] in 76% of 51 cases; Arbesman and colleagues[4] in 84% of 106 cases. In a later study Arbesman[5] rated Pyribenzamine one of "the most effective of all the drugs studied in allergic rhinitis. . . ." *Side effects:* It has been stated that "undesirable symptoms from the use of 50 to 100 mg. doses of Pyribenzamine were rarely of sufficient severity to interfere with its use."[6] Drowsiness, nausea, epigastric distress, vertigo and other side effects—rarely severe—may occur in some patients.

CONTROLS PENICILLIN REACTIONS

Pyribenzamine has been used successfully to control penicillin reactions—especially urticaria and itching. For example, Kesten[7] found that oral Pyribenzamine relieved or suppressed post-penicillin urticaria in 16 of 18 cases; she termed it "a most useful agent in allergic symptoms which follow the administration of antitoxin or penicillin."

RELIEVES ALLERGIC DERMATOSES

Foster[8] reported good results with oral Pyribenzamine in patients with various allergic dermatoses. In another study[9] of 241 such patients, Pyribenzamine was found effective.

C I B A

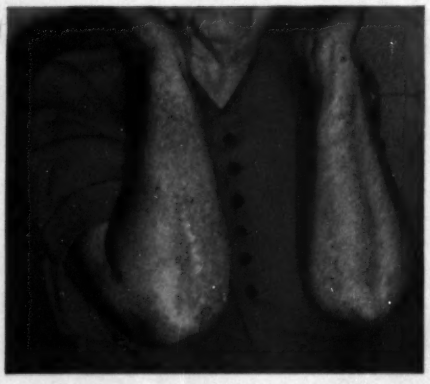
Pyribenzamine 25-mg. tablets now available— for children and for adults who can be maintained on low dosage or who experience side effects from the usual dosage of antihistamines

Supplied: Pyribenzamine hydrochloride 25-mg. and 50-mg. tablets; Pyribenzamine Elixir, 30 mg. Pyribenzamine citrate (equivalent to 20 mg. tripelennamine hydrochloride) per 4-ml. teaspoonful; Pyribenzamine hydrochloride solution (for parenteral use), 25 mg. per ml., in 1-ml. ampuls.

PUBLISHED CLINICAL STUDIES SHOW THOUSANDS OF ALLERGIC PATIENTS RELIEVED BY

Pyribenzamine®

PYRIBENZAMINE HYDROCHLORIDE (TRIPELENNAMINE HYDROCHLORIDE CIBA)
PYRIBENZAMINE CITRATE (TRIPELENNAMINE CITRATE CIBA)



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For complete information on Pyribenzamine ask your CIBA representative or write Medical Service Division, CIBA Pharmaceutical Products, Inc., Summit, N. J.

REPORT ON Pyribenzamine

EFFECTIVE ANTIHISTAMINE

PRODUCT OF CIBA RESEARCH

REPORT ON **Priscoline**

EFFECTIVE PERIPHERAL VASODILATOR

PRODUCT OF CIBA RESEARCH

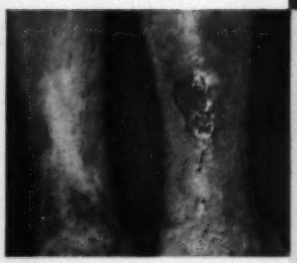
INCREASES PERIPHERAL BLOOD FLOW:

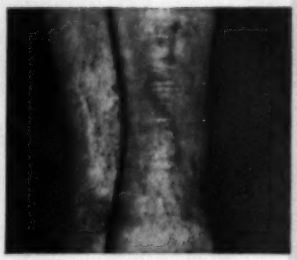
Priscoline reported to be a valuable aid to conventional therapy in peripheral ischemia and its sequelae—pain, loss of function, ulceration, gangrene, other trophic manifestations; Priscoline most effective when vasospasm is prominent but may prove limb-saving even when vasospasm is minimal because it decreases vascular tone, promotes establishment of collateral circulation.

MULTIPLE ACTION:

Priscoline exerts direct vasodilating effect on vessel wall, blocks sympathetic nerves (probably at their terminations in vascular muscle), blocks vasoconstrictive action of circulating epinephrine-like substances.

Side Effects: Certain side effects of Priscoline—"crawling" cutaneous sensation, chilliness with resultant gooseflesh or feeling of warmth—indicate attainment of effective dosage level; occasionally tachycardia, tingling, nausea and epigastric distress, slight hypotensive effect or slight rise in blood pressure may be experienced.



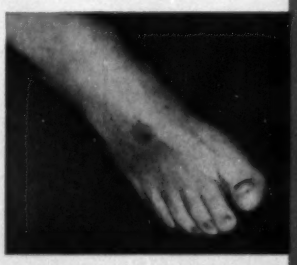


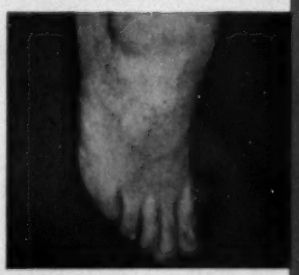
AGE 75. Arteriosclerotic ulceration with erysipeloid reaction and marked inflammation; after administration of oral Priscoline, 25 mg. three times daily, for one week—increased thereafter to 50 mg. four times daily—there is steady improvement, healing in eight weeks. No other medication used.

Priscoline®

FOR COMPLETE INFORMATION on Priscoline ask your CIBA representative or write Medical Service Division, CIBA Pharmaceutical Products, Inc., Summit, N. J. **SUPPLIED:** Priscoline hydrochloride (tolazoline hydrochloride CIBA) is available as 25-mg. tablets (scored), bottles of 100 and 1000; elixir, 25 mg. per 4 ml., in pints; 10-ml. multiple-dose vials, 25 mg. per ml.

Photographs and accompanying clinical data by courtesy of R. I. Lowenberg, M.D., Consultant in Vascular Surgery, Connecticut State Hospital, Middletown, Connecticut.





AGE 68. Arteriosclerosis obliterans cellulitis; sluggish response to saline dressings and procaine penicillin 300,000 units daily; healing speeded by oral Priscoline, 25 mg. four times daily for one week, 25 mg. every three hours thereafter; healing within six weeks.

9/7907

Stage II—The carcinoma extends beyond the cervix and may involve the upper part of the vagina, but has not reached the pelvic wall.

Three patients were placed in Stage II. They were treated with radium for 5000 mcg. hours: the capsules were placed in the lower uterine segment, in the cervical canal, and across the face of the cervix covering the lesion and both lateral fornices. Three weeks later they received 8000 r's measured in air.

All of these patients developed severe slough as a result of the radiation treatment. In one patient the cervix was almost completely destroyed, leaving a huge crater filled with blood, pus and necrotic debris.

The allantomide vaginal cream was used twice daily (one applicator full for each treatment) for ten days, during which the lesion was cleansed of the pus and necrotic tissue. Healthy granulating tissue could be seen starting to fill the craters. The vaginal cream was continued with one application daily until the lesions were apparently healed. In one patient it required four weeks, in another, seven weeks, and in the third patient a very small lesion was still present after ten weeks of treatment. The discharge and odor were adequately controlled and the patient comfortable.

Stage III—The carcinoma has reached the pelvic wall and involves the lower third of the vagina.

Five patients were placed in Stage III. External radiation to the extent of 8000 r's measured in air was used in these patients. Radium treatment as described above was not possible because of the extensive lesions present. Two of these patients were radio resistant.

The allantoin-sulfanilamide 9-aminoacridine vaginal cream was given to these patients to maintain a clean lesion, to control odor and to give as much comfort as possible. One applicator of the cream was administered twice daily until the discharge was brought under control; ten days, on the average, were required. Treatment was continued using one applicator daily for an additional ten days to two weeks. These patients are being maintained on one applicator of the vaginal cream at intervals of two or three days.

Stage IV—The carcinoma extends beyond the limits previously described; may involve the bladder, rectum, or both.

There are ten patients in Stage IV group. Two of these patients had a recto-vaginal fistula. In these patients, external radiation was used to control bleeding, the dosage being adjusted to requirements. Supportive treatment and symptomatic treatment are the most we can do for these patients.

The allantoin-sulfanilamide-9-aminoacridine vaginal cream was given to these patients to control the odor, to maintain a clean lesion and to produce as much comfort as possible. One applicator of the cream was applied twice daily, on arising and at bedtime, until the discharge was brought under control, and then continued once daily.

Six of the patients in this group obtained gratifying results, and four patients continued to complain of marked discomfort.

Note: We want to stress that in all cases the first application of the vaginal cream was given by the physician and the patient was carefully instructed in how to use the medication.

RESULTS

The vaginal discharge and odor associated with carcinoma of the cervix were adequately controlled in a series of 19 patients. Of these 19 patients, 14 expressed gratitude for the relief they received from the treatment. This relief was generally manifested on the third or fourth day of treatment. The discharge was modified and the infection controlled in an average of three weeks. The odor was controlled within one week to ten days, and continued treatment with the allantoin-sulfanilamide-9-aminoacridine cream at intervals of every two or three days was adequate to maintain this control.

COMMENT

It is not our purpose to advocate the use

of allantoin-sulfanilamide-9-aminoacridine vaginal cream as a treatment or a cure for carcinoma of the cervix. As we originally indicated, our search was for a preparation which would accomplish at least three things: (1) control the infection and eliminate the discharge associated with this disease; (2) eliminate the foul odor; and (3) produce a high degree of relief. We felt that if these objectives could be attained, we would then have come upon a treatment which would prove therapeutically profitable in these patients.

Our clinical observations and impressions permit us to say that the allantoin-sulfanilamide-9-aminoacridine vaginal cream has met our challenge and fulfilled the criteria we empirically established.

We are convinced that the allantoin-sulfanilamide-9-aminoacridine vaginal cream is active against bacterial infections, possesses the capacity to eliminate pus and necrotic tissue, to control four odors associated with discharge, and to afford comfortable relief to a majority of patients with carcinoma of the cervix. It is our impression that this combination has a definite use as an adjunct in the treatment of this disease.

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NEWER TRENDS IN DIABETES MELLITUS

A Symposium*

INTRODUCTION
Anthony M. Sindoni, Jr., M.D., Moderator[1],
Philadelphia, Pa.
THE ROLE OF THE ENDOCRINES IN DIABETES
Philip Gerber, M.D.[2],
Philadelphia, Pa.
THE POST-PRANDIAL SUGAR IN DIABETES MELLITUS
Edward M. Bohan, M.D.[3],
Wilmington, Del.
VASCULAR DISEASE IN DIABETES MELLITUS
Dorothy Macy, Jr., M.D.[4],
Philadelphia, Pa.
THE ELECTROLYTE APPROACH IN TREATMENT OF DIABETES
Richard A. Neubauer, M.D.[5],
Wilmington, Del.

INTRODUCTION

Dr. Sindoni: I believe all of you know the seriousness of this condition, diabetes. It is gaining momentum throughout the world, especially in America. I can say that in the seventeen years that I have been at the Philadelphia General Hospital, the fourth largest hospital in America, with 1600 to 1800 registered diabetics, that I am daily becoming more conscious of this condition because it is on the increase, especially as far as vascular diseases are concerned. It seemed, years ago, with the advent of insulin, that we would be able to conquer these associated conditions as retinopathy, coronary disease, and gangrene. Unfortunately, in spite of the advances we have made with insulin, and now the slow-acting insulins, in nutrition, and better and earlier diagnosis of diabetes and its complications, even before the true symptoms of

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diabetes appear, our vascular conditions are on the increase.

Tonight, with the group we have here, we will try to clarify some of the points so that you may get a better idea of this condition known as diabetes mellitus.

There is a school of thought today throughout the world which believes that diabetes is responsible for these associated vascular conditions. There is another school which believes that these so-called conditions with diabetes are only associated with it, and are not related to the disease. Some believe that diabetes is not a disease. They believe it is part of a syndrome, and perhaps that is more clarified in the work of Dr. Richard Neubauer, who has done some interesting work on the renal conditions associated with diabetes. He is Research Consultant on kidney disease at this hospital. He has been able to observe that many of these patients who have nephrosis with a progression of their renal pathology have been able to discontinue their insulin. Why is that? Some have been able to discontinue insulin, even those who have been taking large doses.

Then we go into the endocrine phase of diabetes. Some say that diabetes is an endocrine disturbance. Dr. Philip Gerber will clarify that for you. Also, on methods of examining these diabetics—how do we know when we have a diabetic stabilized? Is the blood sugar the sole criterion in determining the state of control of a diabetic? Is the fasting sugar the sole index, or a post-prandial sugar, or both? That's also a debatable point, and Dr. Edward Bohan, Chief of the Metabolic Department of this hospital, will discuss this phase of the subject. Dr. Dorothy Macy, Jr., of Woman's Medical College, will discuss the vascular aspects of the disease.

First, I wish to introduce Dr. Gerber, who has been associated with me since I went on the staff of the Philadelphia General Hospital. He will speak to you on the relationship of the various endocrine glands in diabetes.

The Role of the Endocrines in Diabetes

Dr. Gerber: Thirty years ago a paper on the role of the endocrine glands in diabetes would have been very much easier to give. In those days diabetes mellitus was considered a disease entity whose etiology, physiology and pathology were well established facts in our medical literature. This, however, is not the case today, and although much has been discovered since insulin was first used on human beings, what we now know about diabetes only proves to us how much more there still remains to be discovered before we can answer the question: "What is the cause of diabetes?"

We are now beginning to get some results from the vast amount of work that is being done in the various clinics and research laboratories interested in what I think is the most intriguing phase of the subject—the role of the various endocrine glands in diabetes.

Many of us are inclined to feel that such a subject is largely theoretical and therefore belongs in the domain of the armchair scientist, rather than part of a seminar presented to hard-working, practical-minded medical practitioners.

However, you must remember that many of the things we accept as facts today were no more than theories when we went to medical school, and many of the things that we were taught to accept as absolute facts have since been questioned. and exist again as only theories today. For example, we were taught, and probably many of you were taught the same thing, that diabetes mellitus is a disease of disturbed sugar metabolism, due essentially to disease of the pancreas. Because of this disease condition of the pancreas, the islands of Langerhans could no longer secrete sufficient amounts of insulin, and the sugar, therefore, accumulated in the blood stream, producing the chain of symptoms known as diabetes mellitus.

Today, however, we feel that these changes in the islands of Langerhans are only a small part of the disturbance resulting in diabetes, in fact, they are prob-

ably more often secondary rather than primary factors in this disease. Today we speak not only of pancreatic diabetes, but also of pituitary diabetes, adrenal diabetes, thyroid diabetes, and diabetes associated with pregnancy, or with obesity, or menopause, thus involving many glands other than the pancreas. This pluriglandular concept of diabetes had its inception with the work of Houssay[1,2] in 1926.

From 1889 until 1926, diabetes had been a so-called "unitarian disease," 1889 being the date when VonMering and Minkowski first produced diabetes experimentally by total pancreatectomy. This seemed to settle the question as to the site of the cause of diabetes, and when, in 1921, Banting and Best isolated insulin, it made the solution to the entire problem of diabetes seem so simple. When, however, Houssay made normal animals more sensitive to insulin by removal of the pituitary gland, he began a chain retion of research that is still going on today, and that has incriminated almost all the other glands of internal secretion in this one symptom complex, diabetes. In 1930 he followed this up by causing experimental diabetes in animals by pancreatectomy, and then making the diabetes less severe by hypophysectomy.

This is the classic Houssay experiment, in which removal of both the pancreas and the pituitary gland produces a mild form of diabetes, fasting producing hypoglycemia and feeding bringing on hyperglycemia. Should crude anterior pituitary extract then be administered to this Houssay animal, it will cause a prompt return of severe diabetes. It therefore became clear that for pancreatic diabetes to manifest itself in the usual way, certain secretions of the anterior lobe of the pituitary gland were necessary.

This work was confirmed by Long, Lukens, and Dohan at the University of Pennsylvania's Research Department, and they were able later to obtain the same effect by adrenalectomy. They removed the pancreas from an animal, causing diabetes, then ameliorated the diabetes by adrenalectomy; and then reinstituted the diabetes by injections of adrenal cortical extract. This would indicate that the maintenance of diabetes after pancreatectomy depends on stimulation of the adrenals by the pituitary gland through its corticotropic hormone.

The Houssay school then injected crude anterior pituitary extract into normal dogs and produced a transient hyperglycemia. This work was carried one step further when Young[3] produced diabetes of long standing in normal animals by the persistent injection of suitable anterior pituitary extracts. More recently, at the University of Pennsylvania, they were able to show that this type of diabetes varied with the number and strength of anterior pituitary extract injections. That is, when small doses were given over a short period of time and insulin therapy was started early enough, the diabetes produced was of a reversible nature, and would disappear shortly after the pituitary injections were stopped. On the other hand, if the daily injections of extract were large enough and were continued for a longer period of time, the diabetes so produced was permanent, and did not disappear when the injections were discontinued.

Histologically, the changes in the islands of Langerhans in the pancreas paralleled the clinical picture produced. In the first group of cases, the islands of Langerhans showed only cloudy swelling, and when the injections of extract were discontinued, the cells returned to normal. In the second group of cases, however, the islands of Langerhans showed hydropic degeneration, which changes were irreversible, and it was in these animals that the diabetes was permanent.

Young and Lukens were, therefore, the first to show that a normal animal could be given pancreatic diabetes by the administration of excessive amounts of hormonal material from an extra-pancreatic organ.

A great deal of clinical significance is being attached to the reversible changes just mentioned. We have always felt that once a person has diabetes, that person

will never be rid of his diabetes; he may be controlled, but never cured. On the basis of these animal experiments, however, it seems logical that the reason we cannot cure our diabetics is because we discover them too late, after the histologic changes in the islands of Langerhans have become irreversible.

This makes it all the more important for us to try to diagnose our cases earlier, and once having diagnosed them, to start insulin therapy earlier. In this manner we may be able to stop the pathological processes in the pancreas before they become irreversible, and with proper control with insulin and diet allow the islands of Langerhans to return to normal.

That such islet lesions do occur in many persons is a fact observed at the postmortem table, and it is entirely possible that they are due to overactivity of the hypophysis. This may be the explanation for the findings of Priscilla White—that there is a higher incidence of diabetes among children who are tall for their age than among those who are of average or less than average height: the height and the diabetes may both be due to increased activity of the anterior lobe of the pituitary gland.

Further investigations made it evident that the potent diabetogenic material in crude pituitary extract was probably growth hormone, but that a minimal level of adrenal cortical function was necessary for the growth hormone to exert its full diabetogenic action. It seems that two anterior pituitary hormones, growth hormone and adrenocorticotropin, are involved in bringing about the metabolic consequences of total pancreatectomy.

Growth hormone is thought to exert its effect in two ways: first, directly upon the pancreatic islet cells, stimulating them to increased insulin secretion, this excessive stimulation of the islets leading to degeneration from overwork and permanent diabetes; and second, an extra pancreatic effect, the inhibition of peripheral oxidation of glucose. This would increase the peripheral need for insulin. The increased secretory activity and ultimate islet cell degeneration seen in the pancreas are then considered to be a secondary phenomenon.

ACTH must be considered with the adrenal cortical hormones, because the effects of ACTH upon carbohydrate metabolism are solely due to the capacity of this hormone to stimulate increased secretion of adrenal cortical hormones, particularly those of the 11-oxygenated type, such as cortisone and hydrocortisone. These steroids raise blood sugar through two major activities: first, by increasing the rate of glycogenesis from protein, and second, by also depressing the rate of tissue utilization of carbohydrate.[4]

Turning now to the adrenal medulla, you are all aware of the acute effect of epinephrine in raising blood sugar. This is accomplished by hepatic glycogenolysis. In addition, however, epinephrine causes a discharge of ACTH from the anterior pituitary gland. Therefore, to the established actions of epinephrine upon carbohydrate metabolism we must add the effects of adrenocortical hormone, namely, increased glyconeogenesis from protein and depressed peripheral oxidation of glucose.

Finally, the effects upon carbohydrate metabolism of thyroid hormone: these are relatively minor, the major effect being upon the rate of intestinal absorption of sugar. Lack of the hormone results in slow absorption and excessive thyroid hormone produces rapid absorption.

One must not forget, also, that the blood sugar level itself can exert an influence upon its own regulators. Hypoglycemia causes a discharge of epinephrine and sets off the eventual adrenal cortical response. Hyperglycemia, per se, is a stimulus to increased pancreatic insulogenesis.

In closing, we must remember what Conn[5] says, that despite all of the newer knowledge, the factor or factors which initiate the diabetic state in man remain obscure. It is this inciting factor which is the elusive one. And, as pointed out by Soskin[6], we should stop referring to insulin as if it were the only hormone concerned with carbohydrate metabolism, and

to diabetes as if it resulted only from a disturbance or disease of the pancreas.

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Dr. Sindoni: Thank you, Dr. Gerber. Our next topic will be delivered by Dr. Bohan: the significance of post-prandial blood sugar. You were formerly taught in treating your diabetics to use a fasting blood sugar as a guide in measuring your insulin dose, as well as prescribing the diet. Now Dr. Bohan will go into detail as to the significance of blood sugars after a meal in helping to guide your diabetic therapy.

SIGNIFICANCE OF POST-PRANDIAL BLOOD SUGAR

Dr. Bohan: As Dr. Gerber has said, we often diagnose diabetes too late. One of the quicker ways to diagnose it is by using the post-prandial blood sugar. This sugar is taken at an interval after a meal: we usually take it two hours, it can be taken at other times, but that seems to be about the best time.

A review of the literature concerning blood sugar tells us that very little attention was paid to the blood sugar taken after meals until Sindoni called attention to the preference of the blood sugar over urine sugar in diabetic control. Sindoni and Gerber examined 35 cases at the Philadelphia General in 1939, and found the post-prandial blood sugar one-half to three hours after the meal did not exceed the fasting sugar level, that is, the top rating of 120 milligrams. Orent-Keiles and Hallman in Washington did some similar studies in 1949 and verified these findings. In 1951 Ackerman and I analysed a series of cases at the Du Pont Company and obtained the same results.

Despite this work, there are many quotations in scientific textbooks and papers about the post-cibal values of the blood sugar. There seems to be a great lack of uniformity throughout the country on what it should be, despite the work that already has been done. Some writers, including Joslin, quote different values in the same book. Joslin, on one page quotes a rise to 160 milligrams after a meal, and, on another page says that percentage drops to normal within approximately two hours, but does not exceed 140. If it rises to 170 sugar appears in the urine. The blood sugar in normal people, according to Joslin, usually reaches its greatest height about half an hour after a meal.

John, Kolmer, Yater, Duncan, Root, White, Marble all have different ideas concerning the height of the sugar after a meal in the normal person. Readings quoted by the American Diabetic Association are also high. In the proceedings of that Association in 1948, it was resolved upon recommendation of an advisory committee of physicians, that the consistent one-hour post-prandial venous blood sugar of 170 mgms. per cent or above plus glycosuria were considered to be indicative of diabetes. John says that in the normal person following each meal there is a rise in the blood sugar level . . . "This rise is not very high, does not last long, from one to two hours at the most, usually one and one quarter to one and a half hours. Thus we speak of a normal, physiologic, post-prandial hyperglycemia" . . .

Kolmer, in 1943, says that hyperglycemia occurs normally after a meal, especially after the ingestion of carbohydrates and he believes that blood sugar determination should be made after a period of at least five hours of fasting, or preferably, in the morning, before breakfast; and there are similar quotations by the men whom I have already mentioned.

From the review of the literature on the subject and this study of Dr. Sindoni's and the others mentioned, it is concluded that the normal blood sugar, post-prandially, at the one to three hour level is not above the normal range of fasting

80-120 milligrams per 100 cc. Therefore, the post-prandial sugar may be used at this level of diagnostic distinction between diabetics and non-diabetics, and this has been adopted by many clinics. A blood sugar over 120 milligrams at the two-hour level, which is the usual time it is taken, justifies a repeat blood sugar. There is always the possibility of some slight laboratory error, and, in most cases, a glucose tolerance test should be done under standard conditions, that is, high carbohydrate diet, preferably 300 grams carbohydrate daily for three days preceding the test. That is very important in doing any glucose tolerance test.

Since the survey done in Oxford, Massachusetts, a few years ago to try to determine the number of diabetics in the country, it was estimated that there are a million undiscovered diabetics. Some more diagnoses could be made by using the post-prandial sugar routinely instead of the fasting sugar. It has been carefully estimated that 11% are missed by using the fasting sugar.

I have here a chart of a glucose tolerance test done a few weeks ago. There is a post-prandial sugar of 126 milligrams in an obese person. Of course, the obesity could have justified a glucose tolerance anyway. We did the test just on a hunch that the 126 might not be normal. It was pretty close to the borderline, but here is the glucose tolerance: 118 fasting, 155 first specimen, 186 second specimen, 184, the third: sugar one plus in the urine on all specimens except in the fasting, where there is a trace.

After making the diagnosis of hyperglycemia an effort should be made to identify the type of diabetes. I don't think we're conscious enough of the different types of diabetes and the help that the post-prandial blood sugar will give in leading us into the diagnosis of these different types. There are many types of cases, but I think the best classification is physiologic in scope, and is made according to the insulin content in the human body, which deficiency may be absolute or relative:

(1) Hereditary deficiency of the beta cells of the pancreas.

(2) Destructions of the beta cells by: (a) Pharmacologic agents, e. g., alloxan. (b) Disease of chronic pancreatitis or tumor of that organ.

(We can usually say "Well, the patient has diabetes," but we must think "That patient might have a carcinoma of the pancreas.")

(3) Exhaustion of the beta cell activity because of an excessive demand for insulin: e.g., the obese type of diabetes.

(4) Deficiency of insulin precursors, as glutathione. Perhaps some of the amino acids may be deficient in the diet or the synthesis may be faulty, and the patient may not be manufacturing enough insulin in the pancreas from the deficiency of elements that make up insulin.

(5) Extra-pancreatic causes may be due to antagonism to insulin from its mates in the glandular system, the anterior pituitary, adrenal cortex, thyroid gland, or to the peripheral inactivation of insulin with failure of the proper end-organ response.

The post-prandial blood sugar is also used by the Philadelphia General Hospital group in treatment. Dr. Sindoni and his group believe that the fasting sugar taken 8 to 12 hours after a meal (that is, after a night's rest) gives no information of the metabolizing power of the patient's insulin and carbohydrates mechanism. Therefore, they have adopted a diabetic 2-hour post-prandial standard of 170-220 mgms. per 100 cc. This is in the average insulin-treated patient, not in the non-insulin treated patient. The height of the latter patient's sugar is no problem before or after meals.

The insulin-treated diabetic has to be kept at a sugar level compatible with his well being with this method of treatment. If he excretes excess sugar in the urine at this level of post-prandial sugar it is disregarded so long as the patient is in good physical condition objectively and subjectively. This method of treatment still

does not place the Sindoni school of thought in the same category as the Tolstoi method of treatment. I think that is important to bring out because it looks like a loose method of treating diabetes, but it is not because the 170-220 level post-prandial isn't too far from the older method of control by observation of fasting sugars.

Tolstoi completely disregards the fasting sugar, post-prandial, or urinalysis, so long as the patient is free of symptoms. He disregards the urine sugar and watches only for acetonuria, or acidosis in any form. In his book "Living with Diabetes" he says "Since there is no evidence that a high blood sugar contributes to infection, that it produces acid intoxication, or is a cause of hardening in the arteries, why worry about the blood sugar or sugar in the urine? Is it worth all the trouble of weighing or measuring diets and going through all sorts of tests and calculations to avoid high sugar when there's no evidence of damage to the diabetic treated with insulin."

Of course, this free method of treatment would be seriously contested by the Joslin school which believes that the blood sugar should be kept as low as possible, in their opinion, probably to avoid damage to the arterial system. I am quoting the Tolstoi and Joslin schools of thought to show you the two extremes.

It is my belief that the Tolstoi and Joslin schools are at the extremes of the rainbow, and that the ideal colors for the diabetic standard lie in between the two: perhaps in the compatible hyperglycemia school of thought of our moderator, Dr. Sindoni, and his staff at the Philadelphia General Hospital.

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Dr. Sindoni: Since the advent of insulin, our mortality seems to be increased as far as vascular deaths are concerned. I know in our wards we find diabetic gangrene very much on the increase. We have not solved that problem: we have not been able to decrease our vascular deaths in diabetes. I include the coronary and gangrene cases when I say "vascular" deaths.

Dr. Dorothy Macy, of the staff of Women's Medical College in Philadelphia, will discuss for us now the degenerative vascular changes commonly associated with diabetes mellitus.

VASCULAR DISEASE IN DIABETES MELLITUS

Dr. Macy: Cardiovascular-renal disease is now the leading cause of death in diabetes mellitus. It accounts for 75.9% of deaths in diabetics, and of these 73.6% are classified as "arteriosclerotic."[1] Under this heading are included coronary atherosclerosis (35.8%), diabetic nephropathy (9.3%), with total renal vascular causes of death (13%), cerebral arteriosclerosis (12.7%), gangrene (1.1%) and "arteriosclerosis, site unassigned" (1.4%). The remaining 0.3% of deaths from cardiovascular-renal disease are classified as due to "other circulatory and rheumatic heart disease."

The incidence of degenerative vascular changes in diabetics is greater than mortality figures indicate, since such changes are usually present to some degree even though they may not be the leading cause of death. The incidence of degenerative vascular changes in diabetics is greater than that in the general population: arteriosclerosis obliterans is eleven times more common in diabetics,[2] and eighty times more common in diabetic than non-diabetic woman;[3] gangrene is forty times more frequent in diabetic than in non-diabetic women over the age of fifty years. Also, on the average, arteriosclerosis obliterans occurs a decade earlier in the diabetic male and two decades earlier in the diabetic female than in their non-diabetic counterparts. Severe renal arteriolosclerosis is one hundred times more frequent in diabetics than in non-diabetics,[4] and there is an increased incidence of coronary atherosclerosis in diabetics with 4% of male and 14% of female diabetic deaths due to thrombosis.

There is no manifestation of vascular disease unique to diabetes. Diabetes

alone is not the only factor predisposing to vascular disease in the diabetic. From the age of thirty-one years on, 79-89% of newly discovered diabetics are overweight. Obesity predisposes to hypertension—systolic hypertension is almost three times, and diastolic hypertension four and one-half times, as frequent in obese as in undernourished men; systolic and diastolic hypertension are six times as frequent in obese as in undernourished women.[3] Gangrene and coronary thrombosis are three times more common in hypertensive than in normotensive subjects.[2]

The recent work of Barach and Lowy on serum $S^{f\ 12\text{-}20}$ lipoproteins[5] has shown these to be elevated in: 1.) 33% of male and 43% of female diabetics; 2.) 40% of overweight diabetics (the presence, not the degree, of obesity was the factor here); 3.) 41% of hypertensive diabetics; and 4.) 45% of diabetics with roentgen evidence of peripheral arteriosclerosis. They also found that elevated serum $S^{f\ 12\text{-}20}$ lipoproteins were correlated with duration of diabetes: with a duration of 0-5 years, the incidence was 29%; after 6-10 years, the incidence was 38%; after 11-15 years, the incidence was 44%. Without a detailed description of their criteria for diabetic control, they state that the incidence of elevated serum $S^{f\ 12\text{-}20}$ lipoproteins was 31% in patients with "good control," 40% in patients with "fair control," and 49% in those with "poor control." Relative to diabetic control, it is essential to bear in mind that this term usually signifies the presence or absence of hyperglycemia and glycosuria, which, per se, are *not* directly related to the incidence of degenerative vascular disease in diabetics[6, 7] Keiding et al[8] found no correlation in young diabetics between serum $S^{f\ 12\text{-}20}$ lipoproteins and duration of diabetes up to 25 years, but the same trend demonstrated by Barach and Lowy in relation to diabetic control. Correlation of elevated serum $S^{f\ 12\text{-}20}$ lipoproteins with the presence of nephropathy was better, and it was best with retinitis. Along these lines it is interesting to note that the fat-tolerance test (rise in serum esterified fatty acids after a fat meal) in the diabetic yields a curve which deviates from normal in a manner generally similar to the deviation of the glucose tolerance test.[9]

While the inference may be drawn that a disturbance in serum $S^{f\ 12\text{-}20}$ lipoproteins exists in diabetes, as well as in obesity, hypertension, coronary atherosclerosis and arteriosclerosis obliterans, the disturbance does not quantitatively parallel the occurrence of degenerative vascular disease, as it should were it the specific etiologic factor. The most one can say is that the patient with such a disturbance is more prone to develop these changes, and that serum $S^{f\ 12\text{-}20}$ lipoproteins parallel the changes better than any other single biochemical change of which we are at present aware.

Is a disturbance in fat metabolism an inherent part of the metabolic pattern of diabetes mellitus? The answer to that question can now be given in the affirmative.[9] By use of C^{14} labelled glucose, it has been shown that there is a six-fold defect in lipogenesis by diabetic rat-liver slices. Correction of that defect is incomplete with addition of insulin, but complete when certain products (in this instance, pyruvate) of normal carbohydrate metabolism are added with insulin. In alloxan diabetic liver slices synthesis of long-chain fatty acids from acetate (2 carbon) and octoanate (8 carbon) cannot be restored to normal by insulin alone. The conclusion was drawn from these data that "the transfer of energy required for fat synthesis is derived mainly from a coupled reaction involving the simultaneous oxidation of some normal carbohydrate intermediate." The same diabetic liver slices could still synthesize cholesterol, however, and the authors pointed out that in diabetes with the reduction of normal fat synthesis from 2-carbon fragments, such fragments are then more freely diverted to the pathways of ketone and cholesterol formation. Thus, normal carbohydrate metabolism is demonstrably an

essential condition for normal fat metabolism.

The juxtaposition of the facts on lipogenesis in diabetic liver slices with the observations on serum lipoproteins and the post-mortem incidence of degenerative vascular disease in the diabetic is provocative, and more informative than a continued preoccupation with hyperglycemia per se. The latter has become reasonably controllable with the introduction of insulin preparations of varying duration and intensity of action—and control of hyperglycemia has *not* resulted in control of vascular degenerative disease. This very fact should forewarn us, in view of the interrelationship between insulin and fat metabolism, that at least that portion of deranged fat metabolism which is amenable to correction by insulin also is not the specific cause of degenerative vascular disease.

Does this have any practical application? Hyperlipemia is largely independent of fat ingestion[10, 11] and low cholesterol or low animal fat diets have not been a successful answer to its occurrence. There is a predisposing factor as yet unidentified which is far more important in the etiology of hyperlipemia than is exogenous fat intake. However, there is no question that excessive fat intake, and excessive alimentation, aggravate degenerative vascular lipemia, and that hyperlipemia when present aggravates degenerative vascular disease. Therefore, it seems advisable and dietetically reasonable to avoid both excessive fat intake (over 100 grams of fat daily) and excessive caloric intake (excess calories must be converted to fat for storage; when lipogenesis is depressed, excess calories favor ketone and cholesterol formation).

There is no known specific therapy for the prevention or dissolution of degenerative vascular disease be it retinal, cerebral, coronary, renal, or peripheral. Intravenous heparin, in 100 mg. doses daily, is being tried by Engelberg et al.[12] in glomerulosclerosis, because it reduces large lipoprotein molecules to smaller molecules of more normal type; the investigators hope to delay the progress of the disease thereby. That work awaits confirmation. Rutin and ascorbic acid, testosterone, and vitamin E for retinopathy have all been found ineffectual. Symptomatic pharmacologic treatment of vasospasm, which is usually present in the collateral branches of vessels undergoing active degenerative changes, is of value and should be employed. Glyceryl trinitrate, Priscoline, Roniacol tartrate, and autonomic ganglionic blocking agents are all effective to some extent. The advisability of sympathectomy for arteriosclerosis obliterans in the diabetic is open to question — Murray feels that it may, in the diabetic, precipitate gangrene; Root feels that it may predispose to subsequent phlebothrombosis.[13]

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THE ELECTROLYTE APPROACH IN TREATMENT OF DIABETES

Dr. Neubauer: May I impress upon you the seriousness of proper management of this complication of diabetes. Until the measurement of sodium and potassium by the Flame photometer, it was not uncommon to have a patient in acidosis and coma who was treated for 12-14 hours with normal saline, glucose, insulin, and

other recognized therapy who responded well until the clinician would turn his back, and the patient would die suddenly. There was no explanation of this until potassium determinations were readily and rapidly available, and it is now known that many of these deaths were preventable, and due to potassium depletion.

Potassium has received considerable attention in the literature in the management of acidosis and coma, and I think everyone is aware of the fact that it has a definite place in therapy. I want to speak to you about potassium lastly this evening, because the problem of proper fluid therapy is necessary before potassium administration is given. We accept too routinely the fact that when we see a patient in acidosis and coma we immediately begin to order insulin, which is undisputably beneficial, and the one most important thing we can do, but then the next part of the routine is the administration of normal saline, or perhaps we switch to glucose and water, or glucose and saline, depending upon which school of thought you follow.

There is, however, a more physiological and practical approach to the problem. We refer to acidosis and coma, but one of the prominent features of this diabetic state is dehydration. How frequently do we think of the severity of the dehydration? It is not generally realized that any time you put an isotonic sodium chloride solution into a patient's body the volume of distribution becomes part of the extracellular fluid or fluid outside the cells, and, therefore, you do not readily furnish body water. One very important factor in the treatment of dehydration is water. Since we can't give sterile water intravenously, which would produce hemolysis, and because a number of people do not believe in using glucose and water initially, I want to propose to you tonight the recent trend of the use of hypotonic saline solutions.

We can break down dehydration into two groups. First, there is the pure water deficit, of which a typical example is a patient who, on a hot day limits fluid intake for a period of 24 hours or so. Then there is the extracellular electrolyte depletion, and the pure example of that is an Addisonian crisis where there is a renal loss of body fluid in isotonic concentration. The commonest group we encounter, however, is a combined water and electrolyte deficit. In the management of acidosis and coma we have already mentioned that normal saline does not readily provide body water. So one may say "Well, I've seen cases for 15 to 20 years, and they've all done beautifully." However, this holds true only if the patient has good kidney function and can excrete the sodium chloride leaving water behind from the isotonic solution, then the water part of the dehydration may be overcome.

Now the need for sodium and chloride in the management of acidosis and coma is three-fold: (1) The volume of the extracellular fluid must be expanded, and one can't expand it with water alone. It must be expanded with the components that are normally there. (2) There must be enough sodium available so that base is present for the CO_2 combining power to expand upon, as the patient responds to therapy, and (3) In order to get an adequate urinary output, enough sodium must be available because one cannot excrete urine without sodium in it.

An important consideration in the choice of a fluid is "Will it meet all the necessary criteria?" We propose half-normal saline. There we give adequate sodium and chloride, but we also give adequate water simultaneously. It is a question of how much base is lost in acidosis and coma, and I think that that can be readily observed clinically and from the history. If a patient goes rapidly into coma precipitated by an infection, and this is perhaps a 12-hour onset, there is very little loss of total body base, and, therefore, more water than base would be needed. If it becomes a long case, e.g., a period of weeks, and the kidneys' ability to manufacture ammonia is working at top speed, then body base has to be drawn upon to excrete the acid radicals. There is then a significant depletion of body

base. As to water loss, most of that is urinary, which is referred to as an "osmotic diuresis," because, as the concentration of glucose is elevated, the diuresis increases. Vomiting may be a complication, and there is continuous loss through the skin and lungs.

At the 1953 Atlantic City meeting of the Society of Clinical Investigation, there was almost unanimous agreement that half normal sodium chloride, that is, half water and half sodium chloride was the solution of choice, and an interesting sidelight is the addition of carbohydrate to this fluid. Fructose seems to be the one of choice. It has been shown that fructose is beneficial, and that this carbohydrate decreases the ketosis without elevating the blood glucose or the urinary glucose and supplies a rapidly available source of carbohydrate to restore the negative balance from the body cells.

Here I would like to mention a word about potassium. Potassium must never be given in acidosis and coma until certain criteria are established, that is, there must be a stable circulation and an adequate flow of urine. As the patient goes into acidosis and coma the kidney function falls to low levels because of dehydration. These people are breaking down body tissue, liberating glycogen as glucose, and liberating nitrogen. Then potassium passes into the extracellular fluid, a good example of this being the fluid which surrounds the heart. Because this medium is contracted, the potassium concentration is elevated, and cases of sudden death can occur from endogenous breakdown.

Potassium should be used, but it is not usually necessary until the acidosis or coma has been present for six to eight hours. Its need may be ascertained by clinical observation, laboratory tests, the electrocardiograph, plus the requisites of stable circulation and adequate urinary output.

INDICATIONS FOR HYSTERECTOMY*

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Almost everyone, at one time or another, experiences some difficulty in arriving at a decision as to whether a certain uterus should or should not be removed. Unfortunately many surgeons operate on symptoms without pathology, or conversely, on minimal pathology without symptoms. This, of course, should be condemned and in order to form a working basis from which one can come to a definite conclusion without much argument, I will undertake to discuss the indications for hysterectomy by dividing them into four rather distinct categories.

As a rule, gynecological surgery is perhaps considered to be the simplest and most gratifying of all major surgery done today. Therefore, practically every surgeon considers himself an expert gynecologist regardless of his knowledge of endocrinology. Somehow, this does not seem right to me or to the thousands of women who are subjected to unnecessary female operations each year. Women are human beings and should be treated as such; the mere presence of a womb and the possibility of a fee are not legitimate indications for hysterectomy. That many surgeons are unfamiliar with the physiology of the reproductive organs is born out by the number of appendectomies and right oophorectomies done in young girls every year. Some surgeons, when viewing the right ovary through an appendectomy incision and seeing the many small cysts scattered over the ovary, just can't resist the temptation of extirpating this poor innocent organ despite the fact that every well trained gynecologist knows fully well that these cysts are physiological in nature and entirely harmless.

I have no axe to grind with those who conscientiously and scientifically consider each case on its own merits and act accordingly. On the other hand, almost any pathologist will tell you confidentially

*Lecture before the Department of Obstetrics and Gynecology, St. Francis Hospital, Wilmington, November 15, 1953.

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that he has a very difficult time finding some excuse for many of the hysterectomies which are done daily in hospitals all over the country. The lowering of the death rate makes the operation available in a number of situations where formerly its risk would have been a contra-indication. The result is a great increase in the number of hysterectomies with a proportionate increase in the number of good and bad results. The bad results have provoked considerable discussion. Miller studied a series of cases done in ten different hospitals in ten different communities, both large and small, in the midwestern states. In 17.4% of patients having hysterectomy, the diagnosis was not confirmed, but the operation was considered justifiable. In 33.1% of patients, there was either no disease or else disease contra-indicating hysterectomy. There has been and always will be considerable discussion about the indications for hysterectomy.

It has been said that a gynecologist is not a gynecologist unless he is skilled in the performance of vaginal hysterectomy. It should also be added that he is not a gynecologist until he has ceased to perform unnecessary hysterectomies, for this operation has become nearly as overdone as the operation of T. & A. and appendectomy.

Before any operation, one should ask himself these questions:

1—Will this operation definitely or almost certainly help this patient?

2—Will the help be of a lasting nature?

3—Is there some lesser procedure involving less risk, trauma and expense which might serve the ultimate purpose just as well?

All of the above questions certainly apply when one considers removal of the womb. To a woman, the womb is not only a functioning organ, it is one of the chief symbols of femininity. She is constantly reminded of this by the recurring menstrual periods and by the womb's important part in reproduction. The endocrine role of the womb has not been proven or disproven but there may be some important pituitary ovarian uterine synergism. Therefore, one must consider and weigh the necessity of hysterectomy in each individual case against the possible far-reaching psychologic and endocrinologic results it may bring. Let us remember this before we urge a patient to have her womb removed on a flimsy uncertain basis. Often these patients haunt the surgeons, the psychiatrist or some other physician for many years afterward.

Bearing the foregoing in mind, I believe each case should be subjected to the following analysis:

1—Severity of disease.

2—Severity of symptoms and mental stability of patient.

3—Age of patient.

4—Parity and desire for pregnancy.

5—Operability and operative risk.

Applying these questions, we might briefly discuss some of the more common maladies for which hysterectomies are done.

The indications for hysterectomy have been divided into four groups: (I) Absolute; (II) Relative; (III) Borderline; and (IV) Questionable.

I—Absolute Indications.

A—Benign absolute indications.

1—Fibromyoma uteri which serves as a true indication under special conditions. These include severe uterine bleeding, necrosis, torsion, pelvic pressure symptoms and pain. If the patient qualifies under the above conditions, the indication is absolute and hysterectomy should usually be preceded by diagnostic curettage to rule out malignancy. Since this is perhaps the most common pathologic entity treated by hysterectomy, let us consider it in some detail.

a—Severity of the disease Myoma uteri cannot be called a serious disease per se. Many women have one or more uterine myomas for years and never know it. They are found at autopsy in about one out of five women, and the fact that a few small symptomless nodules are felt in the uterus is no legitimate

indication for hysterectomy. Malignant degeneration is rare. Sarcoma of the uterus which of course almost always arises in a myoma accounts for only three to four per cent of all uterine malignancies. Any rapid increase in size should make one suspicious of possible malignant changes.

b—Severity of symptoms. This seems to be one of the most important considerations, particularly in the thirty to forty age group.

1—Is the bleeding severe, constant or often recurring?

2—Is the pressure on the bladder or rectum interfering with the normal functions of these organs?

3—Is there considerable back pain or dysmenorrhea which can not be controlled adequately by minor treatments or medicines?

4—Is the patient generally incapacitated to carry out normal duties at home or at her place of employment?

5—Are there episodes of acute pain consistent with torsion of the pedicle?

6—What is the mental stability of the patient?

7—Are many of her complaints on a psychosomatic basis?

c—Age-Myomectomy is preferable if at all possible in the younger age group. In the older age group of forty to forty-five years, expectant treatment often is indicated because it is a well known fact that myomas usually regress in size or may even disappear during and after the menopause.

d—Parity and desire for pregnancy. To me, these are very important considerations.

1—Is the patient married?

2—Does she expect to be married?

3—Does she have or want children?

4—Is the patient willing to put up with the symptoms a while longer in the hope of conceiving and bearing children?

5—Would myomectomy suffice and thus leave the woman her child bearing function?

e—Operability and operative risk.

1—Does the patient have an associated disease which might be aggravated by hysterectomy?

2—Would intra-uterine radium or external irradiation be less dangerous and at the same time accomplish adequate relief after diagnostic curettage to rule out cancer and feel the contour of the endometrial cavity?

2—Adenomyosis, which is frequently an incidental pathologic finding but may sometimes be diagnosed by careful clinical history, serves as a good reason for removal of the uterus. The patients are usually in their late thirties or early forties before symptoms occur and a hysterectomy is a justifiable procedure, the fate of the ovaries being decided on the basis of such factors as age of patient and the presence of ovarian or generalized pelvic endometriosis.

3—Tuberculosis of the endometrium, cervix or otherwise limited genital infection can best be treated by complete excision of the disease. In tubal infection, sterility is the rule since the disease is usually bilateral and removal of both tubes is usually done. There is some difference of opinion as to the advisability of removing the uterus. In view of the impossibility of pregnancy and the frequency of endometrial involvement, it is usually wiser to perform hysterectomy than to trust to the endometrium to throw off the tuberculous disease. One or even both ovaries can usually be conserved unless they too are involved.

B Malignant absolute indications for hysterectomy.

1—Adenocarcinoma of the uterine fundus is treated by total hysterectomy alone or in combination with radiation therapy. Even though there may be

some discussion as to the hows and whens of the surgery or radiation, there can be no doubt that total hysterectomy is the operative procedure of choice and demand, and is our soundest reason for it. Exception to the rule of surgery for final cure of fundal adenocarcinoma may be found in surgically poor risk candidates such as the very aged, very obese, diabetic and cardiac patients.

2—Sarcoma—of the uterus in general, but this disease is somewhat more difficult to diagnose pre-operatively as it is usually an incidental clinical or microscopic occurrence, included with uterine fibroid specimen. These sarcomata, however, may sometimes be diagnosed by biopsy of extruded sarcomatous tissue from the cervix.

3—Carcinomata of the fallopian tubes and ovaries demand in their surgical treatment that hysterectomy be done because of the theoretical and actual dangers of extensions through the uterine lymphatic system. Hysterectomy, therefore, should be done, if total removal of these types of carcinoma is deemed as a cure of the disease.

4—The metastatic extensions from other pelvic organs, namely, the bladder and rectum, which have actually or potentially invaded the uterus, serve as sound indications for hysterectomy. It may occasionally be in order, also, to facilitate removal of other pelvic carcinomata, even though actual invasion has not occurred.

C—Obstetrical absolute indications for hysterectomy.

1—The highly malignant chorionepithelioma, limited to the uterus and adnexa, serves as the malignant cause for hysterectomy in this group. For that matter, even in the presence of vaginal or vulvar metastasis, operation is not necessarily contra-indicated, in view of the occasional degression of such metastases. It may be suggested that roentgenism be used preoperatively in an effort to arrest somewhat the rapid growth of this highly malignant tumor before undertaking abdominal surgery.

2—The Porro type section, with its associated high mortality, is becoming less of a necessity with more moderate supportive therapies, namely, transfusions, sulfa and penicillin medication. The extraperitoneal section and even laparotrachelotomy may be used in preference to a Porro section. However, the grossly contaminated pregnant uterus is still sometimes best treated by section hysterectomy.

3—Uterine apoplexy with Couvalaire uterus which does not resond to stimulation and oxytoxics may demand hysterectomy on the basis of actual uterine necrosis and extensive extravasation of blood into the myometrium. However, one finds that even uteri which at first may appear damaged beyond repair will recover rapidly when enveloped in hot towels, and far fewer wombs are being sacrificed now than were in former years.

4—Placental accreta with placental invasion of the myometrium due to an inadequacy of the decidua is probably best treated by abdominal hysterectomy. In the management of this serious complication, blood should be available for transfusion and the patient should be in the operative delivery room before any attempt is made to remove the adherent placenta. If it is completely attached to the uterus, no forceful efforts at separation should be carried out. Likewise, if the placenta is partially separated and cannot be removed completely because of densely adherent areas, the safest method of treatment is temporary packing of the uterus followed immediately by hysterectomy.

5—Rupture of the pregnant uterus with fragmented necrotic margins and potential infection does not always lend itself well to simple suturing and occasionally demands hysterectomy for cure of the disorder. Especially if the patient has had her quota of children, the decision in favor of hysterec-

tomy is arrived at much more readily.

6—Chronic inversion of the uterus which has not responded to other lines of treatment fall easily into indications for a hysterectomy. Needless to say, manual replacement of the uterus with firm packing of the fundus and vagina should first be tried in all cases.

7—Cervical tears with hematoma of broad ligament. Occasionally, the tear extends into the lower uterus segment rupturing the uterine vessels in this area. This laceration cannot be seen or reached for repair from below since it extends beyond the attachment of the vagina. Even though the wound is repaired vaginally, the uterine vessels continue to bleed supravaginally into either broad ligament, and hematomas as large as small watermelons can develop in a relatively short time. While it is quite possible to repair the laceration by opening the broad ligament, far more frequently, it is more expedient to remove the uterus.

II—Relative Indications.

A—Fibroid tumors of the uterus which show no associated fundal malignancy, abnormal uterine bleeding, torsion, pressure symptoms or pelvic pain may grow to considerable size over a period of years without offering absolute indication for their removal. Many of these cases can be intelligently followed by repeated pelvic examinations and possible diagnostic curettage. If the fibroid uterus shows none of the qualifications listed under absolute indications and if the total size of the tumor is not larger than a three to four months pregnancy, the indication for hysterectomy is slightly less strong and is of a relative nature.

B—Endometriosis is a disease of the child-bearing age. Therefore, conservation of this function is of prime importance and hysterectomy is seldom indicated. If symptoms and progression of the disease warrant laparotomy, one may be able to dissect out the offending cysts and adhesions and preserve the patient her child-bearing function. Oftentimes, it is advisable to remove only the involved adnexa in unilateral cysts and in the majority, there is no recurrence of endometriosis. It should, however, be remembered that continued growth and development of the aberrant endometrium depends upon stimulation by the ovarian hormones. So when endometriosis is encountered in a woman who is approaching the menopausal age and who has already had all the children she desires, it is probable that most surgeons would be more inclined to remove the ovaries, combined of course, with hysterectomy.

C—Prolapse of the uterus, particularly the third degree type and in elderly women, can likely best be treated by vaginal hysterectomy. The first and second degree procidentia of the uterus may, however, be more properly cured by fascial plastic vaginal surgery, such as Manchester operation, than by vaginal hysterectomy.

D—In conjunction with bilateral oophorectomy, if it becomes necessary in the course of pelvic surgery to remove both ovaries for bilateral cystic or other diseases of the ovaries, it is likely preferred that a hysterectomy be also done in order to avoid future possibilities of malposition and tumor in an organ which has lost its menstrual and reproductive functions by bilateral oophorectomy.

E—Ovarian tumors in women at the menopause—At times, it is extremely difficult to determine grossly if a particular cyst is benign or malignant, so if there is ever any doubt, hysterectomy along with removal of the opposite ovary would be more prudent.

F—Controversial uteri—Once in a while, one will see a uterus where no two pathologists will agree on the diagnosis, some feeling that the endometrium has undergone early malignant changes, while others hold that the lesion is merely an exaggerated proliferative phase. We have not arrived

at the ultimate solution of this question, and I doubt if we ever will. I think there always will be differences of opinion about some of these cases. Most everyone removes some of these uteri just as well as I do, and I believe it is the safe thing to do but the possibility of going overboard on this is always a real danger. The late Dr. Halban's often quoted quotation "Nicht carcinoma aber besser aus" would serve best to illustrate one's feeling. Even if one were not certain that the lesion was malignant, it would fulfill so many of the criteria that one would be afraid not to remove it.

III—Borderline Indications.

A—Questionable carcinoma in situ—best followed by repeat biopsies and close repeat examinations. Since this is a slowly progressive disease, at times taking as long as ten years before becoming invasive, one need not be in any particular hurry to remove what otherwise may be a normal uterus. Particularly, if the patient is still in the childbearing age, which most of them are and if she is still desirous of children, should one be especially cautious in establishing a proper diagnosis.

B—Functional uterine bleeding—The patient with severe menometrorrhagia on the basis of hyperplasia of the endometrium who has reached the age of forty years or more and has failed to respond to other methods of treatment becomes a candidate for possible hysterectomy. The decision is only reached after curettement, low doses of desiccated thyroid, substitutional glandular therapy and possibly radiation therapy have failed to give a cure. The hyperplasia carries some potential metaplasia and actual adenocarcinoma dangers in the menopause group and thus the indication for hysterectomy is strengthened. In intractable bleeding in young women, hysterectomy represents surrender on the part of the physician to the demands of the patient and her relatives to do something to stop the bleeding. This type of case can be most trying to the gynecologist's patience and judgment. Hormonal therapy with Stilbestrol, Natural Estrogens or Progesterone often produce satisfactory results and if necessary, may be used to advantage after diagnostic dilatation and curettage. Some men have advocated the use of low dosage irradiation but with the possibility of far reaching effects of this treatment, it should be used only if castration is desired, and then of course, larger doses should be directed to the pelvis.

C—Fibrosis uteri and seedling fibroids jointly are true borderline indications for hysterectomy because neither offer much in the way of complications or difficulties to the patient. Fibrosis uteri slowly becomes a pathologic side-pocket and the diagnosis is returned to the surgeon by the pathologist chiefly because no sound reason for hysterectomy can be found.

D—The Wertheim operation for squamous cell carcinoma of the cervix is being popularized, and in usual hands, I would consider the use of roentgen ray and radium for carcinoma of the cervix superior to any type of hysterectomy. The Wertheim type of hysterectomy is extremely difficult and should only be done by an operator with years of experience, and then on only a relatively few selected cases of carcinoma of the cervix. The salvage from this disease really remains best with adequate roentgenism and radium treatments.

E—The pelvic cripples who suffer from chronic tubo-avarian inflammation with reinfection and reactivation may occasionally become candidates for pelvic surgery. These cases, however, are by the large majority best treated by medical therapies which include diathermy, Elliot treatments, foreign protein injection or possible short courses of sulfa drugs or penicillin. The temptation to clean out the pelvis

is often strong and must be guarded against.

Acute pelvic inflammatory disease is seldom, if ever, an indication for pelvic surgery because chemotherapy or antibiotics often cause complete resolution under specific therapy. If surgery becomes necessary and the tubo-ovarian disease is extensive and bilateral, hysterectomy may become indicated because of the inclusion of the uterus in the inflammatory process and the associated menometrorrhagia so commonly found with pelvic inflammatory disease.

F—Uterine polyps and endometrial fibroids with broad pedicles which cannot be twisted free or clinically deemed too dangerous for twisting are best treated by hysterectomy. It should be emphasized that removal of uterine polyps be accompanied by curettage to rule out malignant changes which commonly occur in the pedicle of the polyp.

G—Symptomatic relief—Blood dyscrasias or systemic or endocrine dysfunctions which produce uncontrollable uterine bleeding may occasionally prompt extirpation of the uterus. An example of this is a patient with idiopathic thrombocytopenic purpura who is continually anemic from vaginal bleeding. The patient is not cured of her basic disease but at least the main bloodletting route is silenced and thus possibly her life is prolonged, giving her further chances for a cure.

IV—Questionable Indications.

A—Diffuse varicose veins in the broad ligaments may need hysterectomy plus ligation for cure in a certain few select cases.

B—The very rare case of dysmenorrhea which has not been cured by medical therapies and vaginal uterine procedures may become a candidate for presacral sympathectomy and even more rarely a hysterectomy. This would truly be a borderline indication as would be a hysterectomy for retrodisplacement or sterilization without associated disease indicating the procedure.

C—Endocervicitis—In the absence of a lesion in the corpus, it is difficult to reconcile oneself to the idea that hysterectomy plays any part in the management of cervicitis. Cauterization, conization, and if necessary, amputation are readily available and simple measures.

D—Idiopathic pelvic pain—This is usually psychosomatic in nature and rarely, if ever, relieved by the removal of a normal uterus unless this organ should be the seat of her anxiety neurosis, such as fear of pregnancy, etc. However, this type of pain responds far more readily to psychotherapy, sedation, pelvic diathermy, etc. Even presacral sympathectomy rarely cures this syndrome, since one must first treat the mind before healing the body.

E—Cystocele and rectocele in young women. Vaginal hysterectomy should never play any part in the repair of cystocele and rectocele in women under thirty-five years of age. These cases all respond well to anterior and posterior repair along the lines of the Manchester technique but without amputation of the cervix for obvious reasons. Very frequently, the patient delivers subsequently from below with very little trauma to her operative site.

F—Ectopic pregnancy. Rarely should there ever be need for removing the uterus except possibly following rupture of an interstitial pregnancy with massive hemorrhage. Usually the tube harbors the pregnancy and most often it is only necessary to sacrifice this organ, though at times, it also becomes incumbent to remove the adjacent ovary.

In closing, may I again repeat: most gynecological surgery is easy, let us also take it easy on our patients.

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+ Editorials +

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OUT IN THE OPEN

When we came to Delaware just forty years ago we found here some fee-splitting, more than was good for the profession and for the public. We regard fee-splitting as the most damnable practice imaginable; it is nothing more or less than the purchase and sale of sick people!

Due primarily to the influence of the American College of Surgeons this pernicious practice was gradually eliminated here, and for the last 20-25 years we have not heard of any fee-splitting in this state, a status which we feel sure will continue ad infinitum.

But in some other states it has persisted and the College is now cracking down on these areas, as witness the following story from the *Baltimore Sun* of May 3, 1954:

Cleveland, May 2 (AP)—The American College of Surgeons today told its Iowa Fellows to prove they do not split fees or be expelled from the organization.

The College is composed of 19,000 surgical specialists throughout the nation.

Its Board of Regents voted that the group's more than 200 Fellows from Iowa be required to submit their financial records to audit by certified public accountants to prove there was no fee-splitting. Any member refusing to submit to an audit would be given an opportunity to resign, or be ousted from the organization.

Predicts Action

The action was taken on the request of a small group of Iowa members.

Dr. Evarts Graham, of St. Louis, chairman of the Board, predicted similar action would be taken in other states and "spread like a grass fire" in ridding the nation of the practice.

He defined fee-splitting as "any form of inducement (taken by a physician) to refer a patient to a surgeon." He added that when fee-splitting is practiced, usually one-third to one-half of the surgeon's fee goes to the general practitioner or referring doctor.

In most cases, he said, the referring doctor does not inform the patient of his part of the fee.

The College, in a statement announcing the policy, said that "Iowa has been a long time trouble spot on the question of fee-splitting."

At a meeting of the Iowa Medical Society in Des Moines last week, sixteen Iowa Fellows of the College voted to ask the Board to take action requiring Iowa members to submit their financial records to C.P.A. scrutiny.

L'envoi: Caveat emptor!

Gamma Globulin Supply For Physicians

The Federal Office of Defense Mobilization will continue to control the distribution of G.G. in 1954.

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G.G. may be secured from the regular sources as follows on the signature of a licensed physician:

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The G.G. you receive for Measles and Infectious Hepatitis may be labelled "Polio Immune Globulin" or "Immune Globulin." These substances are identical and may be used interchangeably.

(2) for *Poliomyelitis:*

G.G. will not be used on family or intimate contacts of cases, inasmuch as such use has proven of no avail.

All Polio G.G. will be distributed by the State Health Officer for use when indicated in outbreaks of Polio in Camps, Institutions, etc.

OBITUARY

RICHARD C. BEEBE, M. D.

Dr. Richard C. Beebe, a past president of the Medical Society of Delaware and past commander of the Delaware American Legion, died on April 9, 1954, in the Beebe Hospital which, with his brother, Dr. James Beebe, he founded in 1916.

In failing health for the past two years, he had been a hospital patient since early February, and had been critically ill for the past month.

Dr. Beebe was born in Lewes in 1890, the son of the late Richard and Temperance Jane Megee Beebe. He was graduated from Lewes High School and, in 1913, received his medical degree from the Jefferson Medical College, Philadelphia.

When World War I began for the United States, he joined the American Expeditionary Forces, serving as captain with the Pennsylvania medical unit at base hospital No. 10 in France, and on the staff of the surgeon general. He was elected to the American College of Surgeons in 1928.

He was instrumental in founding several lower Delaware posts of the American Legion, including the Sussex Post, Henlopen, and Lewes Post No. 17, and in 1937 was a delegate to the American Legion convention held in Paris.

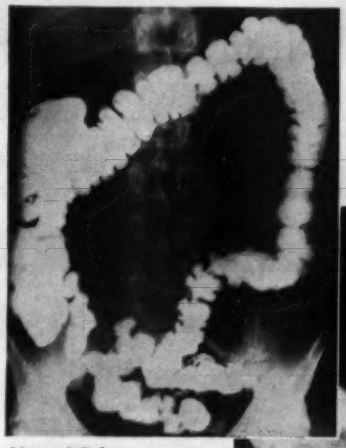
He was a charter member and past president of the Lewes Rotary Club, a charter member of the Rehoboth Country Club, a member of the board of directors of the Sussex Trust Company, and a member of the Lewes and Rehoboth Building and Loan Association. He belonged to Jefferson Lodge, A. F. and A. M., of Lewes.

In May, 1952, he and his brother were honored at the annual commencement exercises of the hospital's school of nursing, and portraits of the two physicians were presented to the hospital as a gift of friends.

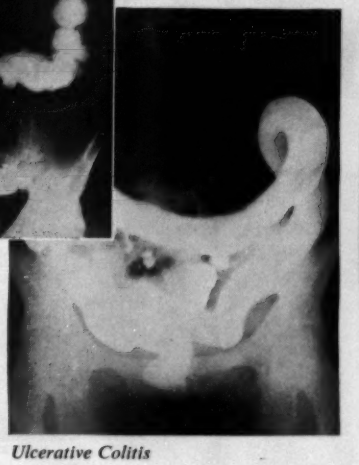
In addition to his brother, survivors include: his wife, Mrs. Edna Thompson Beebe; three daughters, Mrs. R. Edward Moore, Jr., and Mrs. Harry F. Frazier, of Lewes, and Mrs. George Roth of Detroit, Mich.; two sisters, Mrs. G. Herbert Orton, Sr., and Miss Anna Beebe, of Lewes; and seven grandchildren.

Funeral services were held on April 13th in the Atkins Funeral Home, Lewes, the Rev. A. Edward Dougherty, pastor of the Bethel Methodist Church, officiating. Members of the Lewes Post of the American Legion provided an honor guard. Interment was in the Lewes Methodist Cemetery.

No drug having been thus far found in the treatment of tuberculosis which kills all tubercle bacilli, the objectives of drug treatment in this disease still fall short of the eradication of all infecting organisms. William B. Tucker, M.D., Annals of Internal Med., Nov., 1953.



Normal Colon



Ulcerative Colitis

Atonic Colon

Smoothage and Bulk in Correcting Constipation

To initiate the normal defecation reflex, the "smoothage" and bulk of Metamucil® provide the needed gentle rectal distention.

Once the habit of constipation has been established, due to any of a large number of causes, it becomes a major problem. Self-medication with irritant or chemical laxatives, or repeated enemas, usually causes a decreased, sluggish defecation reflex and may result in its complete loss.

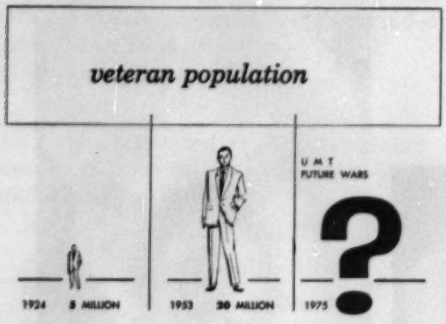
Rectal distention is a vital factor in initiating the normal defecation reflex, and sufficient bulk is thus of obvious importance in restoring this reflex. Metamucil provides this bulk in the form of a smooth, nonirritating, soft, hydrophilic colloid which gently distends the rectum and initiates the desire to evacuate. Metamucil demands extra fluid, imparting even greater smoothage to the intestinal contents.

It is indicated in chronic constipation of various types—including distal colon stasis of the "irritable colon" syndrome, the atonic colon following abdominal operations, repressions of defecation after anorectal surgery and in special conditions such as the management of a permanent ileostomy. Metamucil is the highly refined mucilloid of Plantago ovata (50%), a seed of the psyllium group, combined with dextrose (50%) as a dispersing agent.

The average adult dose is one rounded teaspoonful of Metamucil powder in a glass of cool water, milk or fruit juice, followed by an additional glass of fluid if indicated.

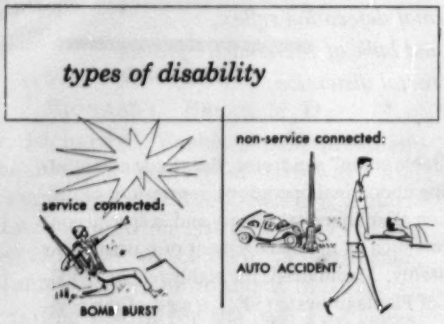
Metamucil is supplied in containers of 4, 8 and 16 ounces. It is accepted by the Council on Pharmacy and Chemistry of the American Medical Association. G. D. Searle & Co., Research in the Service of Medicine.

In Viewing the VA Medical Program . . .



The U. S. veteran population now includes about 40% of all adult males. Under existing legislation, the federal government is obliged to provide "free" medical care for many of these veterans, if they request it. The medical profession questions the soundness of providing medical care at federal expense to veterans with non-service-connected disabilities. It is likely that by 1975 the U. S. will truly be a "nation of veterans." If the VA medical program continues to accept responsibility for the care of veterans with service-connected and non-service-connected disabilities alike it is difficult to see how a complete federal health program can be avoided.

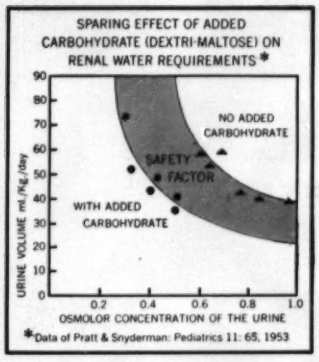
In Viewing the VA Medical Program . . .



The medical profession fully endorses and supports the medical program of the Veterans Administration through which veterans receive medical care and hospitalization without cost for illnesses or injuries incurred as a result of military service (left). It is felt, however, that the federal government should not assume the responsibility for the medical care of veterans whose disabilities are incurred in civilian life and which have no relationship to their military service.

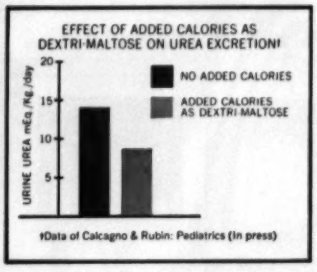
DEXTRI-MALTOSE *formulas*

provide important physiologic safeguards



Added renal safety. When the effective carbohydrate, Dextri-Maltose®, is added to cow's milk formulas, the infant's water requirements are reduced. This provides an added margin of safety against dehydration. In addition, the load on the water excretory capacity of the infant's immature kidneys is reduced.[1,2]

The margin of renal safety is especially important since various stresses and handicaps have been shown to influence the infant's fluid balance and renal capacity.[1,3,4,5]



Better nitrogen retention. The addition of adequate carbohydrate (Dextri-Maltose) to cow's milk formulas increases the infant's nitrogen retention and promotes the efficient use of nitrogen for growth,[2] causing a reduction in the excretion of urea and lightening the load on the infant's kidneys.

Ample carbohydrate is provided in a milk and water mixture by inclusion of 4 to 5% of Dextri-Maltose—or 1 tablespoonful to each 5 or 6 fluid ounces of formula.

With a record of forty-three years of outstanding clinical success, no other carbohydrate has earned such world-wide acceptance and confidence in its constant dependability as Dextri-Maltose.

1. Pratt & Snyderman: Pediatrics 11: 65, 1953; 2. Calcagno & Rubin: Pediatrics (in press); 3. Calcagno, Rubin & Weintraub: J. Clin. Investigation 33: 91, 1954; 4. Cooke, Pratt & Darrow: Yale J. Biol. & Med. 22: 227, 1950; 5. Gamble: J. Pediat. 30: 488, 1947; 6. Rappaport: Am. J. Dis. Child. 74: 682, 1947.

DEXTRI-MALTOSE

the carbohydrate of choice for infant formulas

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